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THE CHEMISTRY OF CRUDE DRUGS

THE CHEMISTRY OF CRUDE DRUGS

AN ELEMENTARY TEXTBOOK FOR STUDENTS OF PHARMACOGNOSY

BY

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PREFACE.

WHILST it is hoped that this book will prove useful to all who wish to gain a general acquaintance with the constituents of drugs of natural origin, it has been written primarily for pharmaceutical students.

It is very necessary that pharmaceutical students should have a systematic, if elementary, knowledge of the chemistry of drugs, and we have ourselves felt the lack of a suitable textbook on the subject. It has been our object to produce a small book which can be used in conjunction with the ordinary textbooks of materia medica, all of which are concerned largely with the morphological characters of drugs. Bearing in mind the type of reader for whom the book has been written, we have endeavoured throughout to assume no more than an elementary knowledge of organic chemistry.

Detailed directions for the performance of a considerable amount of practical work are given in smaller type. Most of the practical exercises described are regularly carried out by students in the laboratories at this college.

We have consulted a number of standard works, notably the British Pharmaceutical Codex, Allen's *Commercial Organic Analysis*, Lewkowitsch's *Chemical Technology and Analysis of Oils, Fats and Waxes*, Henry's *Plant Alkaloids*, Finnemore's *Essential Oils*, and Tschirch's *Handbuch der Pharmacognosie*. Most of the recent information given has been obtained from original papers. Whilst not wishing to over-

burden the book with references, a few original investigations have been referred to in footnotes. Most of these are easily accessible, and are of sufficient general interest to warrant the reading of them by students who wish to pursue the subject further.

It may be pointed out that the chemical investigation of plant and animal products is a subject which presents exceptional experimental difficulties, with the result that, even in the case of the better-known drugs, various authorities may differ widely on the question of their chemical composition. In such cases we have attempted to select the most commonly accepted and best substantiated information. Investigators frequently assign, to natural products of unknown constitution, complex molecular formulæ which are derived simply from the results of quantitative estimations of the elements. Such formulæ are reproduced from time to time in this book, but must obviously be accepted with reserve.

We are indebted to the editor of the *Pharmaceutical Journal* for permission to make use of the subject-matter of a series of articles on "The Constituents of Crude Drugs," which we wrote for educational numbers of the Journal.

Our thanks are due to Mr. A. O. Bentley, Ph.C., for his help and encouragement during the preparation of the book, and to Mr. W. A. Broom, B.Sc., A.I.C., for advice in connection with the biological standardisation of drugs, and for information on vitamins.

J. E. D.
G. E. T.

University College,
Nottingham,
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CHAPTER I.

INTRODUCTION.

From ancient times, substances obtained from plants or animals by simple processes which do not involve the isolation of pure compounds have been employed in medicine. Such " crude drugs " and galenicals prepared from them are still widely employed, although many of them have been replaced, to a greater or lesser extent, by pure medicinal chemicals, which are either isolated from natural sources or prepared synthetically. Thus the pure alkaloid morphine (or its salts) is used for purposes for which, a century or so ago, opium or its preparations would have been invariably employed.

The advantages of the use of a pure chemical compound in medicine are many and obvious, since the physiological effect of such a compound is fixed and definite, and is not complicated by such extraneous factors as variations in quality and the presence of variable amounts of other physiologically active substances. There are, however, many reasons for the continued use of crude drugs and galenicals. First, there is the fact that the nature of the active constituents of many crude drugs is still unknown. Secondly, there is the economic question ; for even where the active constituent of a drug has been identified and isolated, it may not be possible to produce it, either from the plant or synthetically, at a price which can compete with that of active preparations of the drug. Finally, many crude drugs provide natural mixtures of medicinal substances which produce a therapeutic action which is so desirable and well established as to make it unnecessary to attempt the artificial preparation of similar mixtures.

For the study of pharmacognosy, drugs are usually classified according to their morphological nature. This method

of classification is the only one practicable when dealing with macroscopic or microscopic diagnostic characters, or with the detection of substitutes or adulterants. The morphological classification of drugs is, however, unsatisfactory when we come to consider the chemical constituents. Thus, alkaloids are found in leaves ; they are also found in roots ; essential oils occur in all parts of plants ; and so on. It will be seen, therefore, that in order properly to appreciate the chemistry of drugs, it is almost essential that the constituents should be made the subject of special and independent study.

Enzymes and enzyme action in drugs.—The organic constituents of plants and animals are produced as a result of complex chemical changes which cannot, as a rule, be reproduced in the laboratory. Such substances as carbohydrates and glucosides, which are elaborated by plants from simple materials at ordinary temperatures, can only be synthesised artificially by methods involving the use of reagents and conditions not found in the vegetable kingdom.

The chemical changes which take place in living organisms are frequently the result of the catalytic action of certain substances, known as enzymes. The resemblance between the action of enzymes and that of ordinary catalysts is almost complete. As in the case of inorganic catalysts, a very small quantity of an enzyme is capable of bringing about chemical change in a relatively enormous amount of material, and, in fact, there seems little reason to suppose that under ideal conditions the action of the enzyme should not continue indefinitely. As an example, it may be mentioned that the enzyme invertase has been shown to be capable of converting more than 100,000 times its weight of sucrose into invert sugar. In practice, ideal conditions are never realised, and secondary reactions invariably result in gradual loss of enzymic activity. As in the case of many inorganic catalysts, the action of enzymes is selective—that is to say, a particular enzyme is only capable of bringing about one, or at the most one type of, chemical change. Enzymes are extremely difficult to isolate from the organism, and it is doubtful whether any enzyme has been obtained in a state of purity. Such as have been examined are amorphous, generally nitrogenous, colloidal substances, and their activity is doubtless partly due to the large surface presented by the colloidal particles. It is hardly necessary to point

out that enzymes, though the products of living organisms, are themselves lifeless.

Different enzymes act best at temperatures varying between about 35° and 45°, and are usually rendered inactive by heating at 100°. The most favourable temperature for the action of any particular enzyme is known as its " optimum temperature."

As the chemical structure of enzymes is unknown, no classification based on constitution is possible, but for convenience they may be divided into groups according to the types of chemical change which they accelerate, such as hydrolysis, fermentation, or oxidation. Among enzymes producing hydrolysis may be mentioned invertase, which hydrolyses cane sugar ; the lipases, which hydrolyse fats ; and prunase (p. 33), which hydrolyses the glucoside of cherry-laurel leaves. Pepsin (p. 131) and trypsin (p. 132), which occur in the digestive juices of animals, belong to the class of enzymes which break up the protein matter of food into substances which are more soluble and therefore of greater use to the organism. Zymase is a typical fermenting enzyme, bringing about the alcoholic fermentation of sugars. Rennin is a coagulating enzyme, which precipitates the proteins of milk, forming curds and whey. Some enzymes cause changes of colour in flowers and cut fruit, whilst others act on tannins forming products, such as phlobaphenes, which give the red colour to many astringent drugs (kino and acacia bark, for example). Examples of other changes in drugs, brought about or accelerated by enzymes, will be found in later chapters.

The presence of enzymes renders special care necessary in the collection, drying, and storing of drugs, since lack of adequate precautions may result in the inhibition of beneficial reactions, or the initiation of deleterious ones.

The active constituents of the dry drug may not be present in the fresh plant, but may be formed by enzyme action during the process of drying. In such cases the fresh drug is slowly dried at a temperature favourable to enzyme action. Orris root and vanilla pods are examples of drugs in which such changes take place. The latter, when fresh, contain coniferin, which, by the action of a hydrolysing enzyme, is converted into coniferyl alcohol, this being then oxidised by a second enzyme to form vanillin.

In the case of other drugs, the medicinal constituents may be destroyed during drying, unless special precautions are taken to prevent enzyme action. One method of preventing undesirable changes is by drying at a higher or lower temperature than that at which enzyme action readily takes place. By this method the enzyme is not necessarily destroyed, but may be merely temporarily inactivated, so as to be able to resume its activity when moisture and a suitable temperature are again available. Dried drugs will, if exposed to air, reabsorb some 12 per cent. of moisture, this amount being sufficient for the renewal of enzyme action. If enzymes still remain in the dry drug, and their action is to be avoided, it is essential that the drug be stored in air-tight containers, preferably over a dehydrating agent such as quicklime.

The process known as " stabilisation " has an advantage over the one above described, in that the enzyme is permanently inactivated, and can therefore cause no further changes in the drug, or in galenicals made from it. The process consists in submitting the fresh drug for a short time to the action of alcohol vapour under pressure, or to the action of superheated steam. The stabilised drug is then dried in the ordinary way. This method has been recommended for valerian root, and for drugs containing glucosides or volatile alkaloids.

CHAPTER II.

SIMPLE ALIPHATIC ACIDS.

The simplest organic acids are those of the so-called "fatty acid" series, derived from the paraffin hydrocarbons by substitution of the carboxyl group, $-COOH$, for a hydrogen atom. Many of these acids occur in nature, either in the free state or in combination. The first nine members of the series are :—

Formic acid, $H . COOH$.
Acetic acid, $CH_3 . COOH$.
Propionic acid, $CH_3 . CH_2 . COOH$.
$C_3H_7 . COOH$ { Butyric acid, $CH_3 . CH_2 . CH_2 . COOH$.
Iso-butyric acid, $(CH_3)_2CH . COOH$.
$C_4H_9 . COOH$ { Valerianic acid, $CH_3 . CH_2 . CH_2 . CH_2 . COOH$.
Iso-valerianic acid, $(CH_3)_2CH . CH_2 . COOH$.
Optically active valerianic acid, $CH_3 . CH_2 \diagdown \atop CH_3 \diagup \!\!> CH . COOH$.
Trimethyl acetic acid, $(CH_3)_3C . COOH$.

Iso-valerianic acid, $(CH_3)_2CH . CH_2 . COOH$, occurs in the form of its bornyl ester (see borneol, p. 102) in the fresh volatile oil of valerian rhizome. As the drug dries, the ester becomes decomposed, by an enzyme present, with formation of free iso-valerianic acid, to which the unpleasant odour of the dried drug is due. Valerian rhizome is also said to contain bornyl formate and butyrate.

The fatty acids, like members of all homologous series, show a gradual transition in physical properties with increase in molecular weight. The lower members are volatile liquids with pungent odours, but as the series is ascended the acids

become less volatile, and their odours become less pungent and more fat-like. Capric acid, $C_9H_{19} . COOH$, and the fatty acids of higher molecular weight, are waxy solids.

Many higher members of the fatty acid series occur in the form of glycerides in fats and fatty oils, and as esters in waxes (*q.v.*). The following are of particular importance in this respect :—

Lauric acid, $C_{11}H_{23} . COOH$.
Myristic acid, $C_{13}H_{27} . COOH$.
Palmitic acid, $C_{15}H_{31} . COOH$.
Stearic acid, $C_{17}H_{35} . COOH$.
Arachic acid, $C_{19}H_{39} . COOH$.
Lignoceric acid, $C_{23}H_{47} . COOH$.
Cerotic acid, $C_{25}H_{51} . COOH$.
Melissic acid, $C_{29}H_{59} . COOH$.

It is noteworthy that these and most other acids obtained from fats and fatty oils are normal acids—that is, their molecules contain a single straight chain of carbon atoms. Palmitic and stearic acids melt at 62° and 69° respectively.

Certain unsaturated acids, closely related to the higher fatty acids, also occur as glycerides in fats and oils. The most important of these is *oleic acid*, $C_{17}H_{33} . COOH$, an oily liquid, the structural formula of which is

$$CH_3 . [CH_2]_7 . CH : CH . [CH_2]_7 . COOH.$$

By the action of certain reagents, oleic acid is converted into solid *elaidic acid*. Oleic and elaidic acids are geometrical isomers, and, as such, each of them may be represented by one or other of the following formulæ :—

$$\begin{array}{l} CH_3 . [CH_2]_7—C—H \\ \qquad\qquad\quad \| \\ COOH . [CH_2]_7—C—H \end{array} \qquad \begin{array}{l} CH_3 . [CH_2]_7—C—H \\ \qquad\qquad\quad \| \\ \qquad\qquad H—C—[CH_2]_7 . COOH. \end{array}$$

Jecoleic acid, $C_{18}H_{35} . COOH$, is probably a homologue of oleic. More highly unsaturated acids are *linolic*, $C_{17}H_{31} . COOH$, *linolenic*, $C_{17}H_{29} . COOH$, and *therapic*, $C_{16}H_{25} . COOH$, the molecules of which contain two, three, and four double bonds respectively. *Ricinoleic acid*, $C_{17}H_{33}O . COOH$, which occurs in combination in castor oil, is a hydroxy-derivative of oleic acid of the structural formula

$$CH_3 . [CH_2]_5 . CH(OH) . CH_2 . CH : CH . [CH_2]_7 . COOH.$$

Di- and tri-basic acids.

Among the commoner vegetable acids are certain dibasic acids, of which the simplest is oxalic.

Oxalic acid, $\begin{matrix}\mathrm{COOH}\\ |\\ \mathrm{COOH}\end{matrix}$, occurs very commonly in plants in the form of its calcium salt. Rhubarb rhizome, for example, contains about 7 per cent. of calcium oxalate.

Succinic acid, $\begin{matrix}\mathrm{CH_2 \cdot COOH}\\ |\\ \mathrm{CH_2 \cdot COOH}\end{matrix}$, a homologue of oxalic, occurs in certain plants, but is of less pharmaceutical interest than its derivatives, malic, tartaric, and aspartic acids.

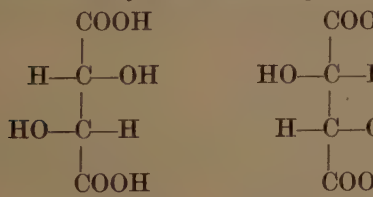
Malic acid, or hydroxy-succinic acid, $\begin{matrix}\mathrm{CH_2 \cdot COOH}\\ |\\ \mathrm{CH(OH) \cdot COOH}\end{matrix}$, occurs in unripe fruits, such as apples and grapes. Calcium malate is present to the extent of 25 per cent. in euphorbium resin.

Tartaric acid, or dihydroxy-succinic acid,

$$\begin{matrix}\mathrm{CH(OH) \cdot COOH}\\ |\\ \mathrm{CH(OH) \cdot COOH}\end{matrix}$$

occurs in considerable quantities in many fruits, such as grapes, raisins, tamarinds, and prunes, both in the free state and in the form of its acid potassium salt. Tamarind pulp contains about 10 per cent. of free tartaric acid and 8 per cent. of acid potassium tartrate.

Tartaric acid contains two asymmetric carbon atoms, and consequently exists in several isomeric forms, which may be represented by the following configurational formulæ :—



d-Tartaric acid — *l*-Tartaric acid

Racemic acid (a crystallographic compound of the *d*- and *l*-forms in equal proportions. Inactive by external compensation).

Meso-tartaric acid (optically inactive by internal compensation).

The naturally occurring acid is dextro-rotatory, but it is sometimes accompanied in plants by varying quantities of racemic acid.

Tartaric acid of commerce is manufactured from " argol," a brownish solid, consisting mainly of acid potassium tartrate with smaller quantities of calcium tartrate, which is deposited in the vats during the production of wines by fermentation of grape juice. The argol is suspended in hot water and neutralised with chalk, when calcium tartrate is precipitated, leaving normal potassium tartrate in solution :

$$2KHC_4H_4O_6 + CaCO_3 = CaC_4H_4O_6 + K_2C_4H_4O_6 + H_2O + CO_2.$$

By the addition of calcium chloride, the potassium tartrate is decomposed, with precipitation of a further quantity of calcium tartrate :—

$$K_2C_4H_4O_6 + CaCl_2 = CaC_4H_4O_6 + 2KCl.$$

The whole of the calcium tartrate is suspended in water and treated with the theoretical quantity of dilute sulphuric acid, when tartaric acid is liberated :—

$$CaC_4H_4O_6 + H_2SO_4 = H_2C_4H_4O_6 + CaSO_4.$$

After filtering off the calcium sulphate, the clear solution of tartaric acid is evaporated to crystallisation.

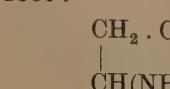
Reactions of tartaric acid and tartrates.—1. Observe that tartaric acid chars readily when heated alone, or when gently warmed with concentrated sulphuric acid.

2. Tartaric acid is a reducing agent. Prepare an ammoniacal solution of silver hydroxide by adding very dilute ammonia to silver nitrate solution in a clean test tube, drop by drop, until the precipitate first formed just redissolves. Then add a solution of a neutral tartrate (such as Rochelle salt, $NaKC_4H_4O_6, 4H_2O$), and warm gently. Metallic silver is deposited on the sides of the tube as a mirror.

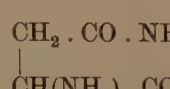
3. Add calcium chloride to a neutral solution of a tartrate. Calcium tartrate is precipitated, either immediately or on shaking. Show that the precipitate dissolves on addition of either hydrochloric or acetic acid.

4. Mix concentrated solutions of tartaric acid and potassium chloride and shake well. Acid potassium tartrate, being sparingly soluble in water, crystallises out. Show that normal potassium tartrate is readily soluble.

Aspartic acid, or amino-succinic acid, occurs in the form of its amide, *asparagin*, in asparagus, and in marshmallow root :—

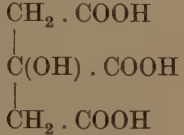


Aspartic acid



Asparagin

Citric acid is a hydroxy tribasic acid which occurs in the fruits of various species of *Citrus*, notably the lemon, lime, and bergamot. It is usually obtained from lemon juice, in which it is present to the extent of 7-9 per cent.



Citric acid

In the manufacture of citric acid, the juice is boiled to precipitate albuminous matter, which is removed. The clear juice is neutralised with chalk, and the calcium citrate produced is then separated from the hot liquid by filtration :

$$2C_6H_8O_7 + 3CaCO_3 = Ca_3(C_6H_5O_7)_2 + 3CO_2 + 3H_2O.$$

The calcium citrate is suspended in water, and treated with the theoretical quantity of dilute sulphuric acid :—

$$Ca_3(C_6H_5O_7)_2 + 3H_2SO_4 = 2C_6H_8O_7 + 3CaSO_4.$$

After filtering off the calcium sulphate, the solution of citric acid is evaporated to crystallisation.

Reactions of citric acid and citrates.—1. Heat citric acid alone, and note the charring and evolution of pungent vapours. Show that citric acid, unlike tartaric, does not char with concentrated sulphuric acid on gently warming.

2. Calcium citrate is less soluble in hot water than in cold. Add calcium chloride to a neutral solution of a citrate. No precipitate forms on shaking in the cold, but on boiling for a minute or so, a crystalline precipitate of calcium citrate is produced.

CHAPTER III.

FATS, FATTY OILS, AND WAXES.

The fats obtained from the adipose tissue of animals, and the fatty oils present in the seeds of plants, are so closely related that in some cases substances of the two classes may be almost indistinguishable from one another. Fats and fatty oils were amongst the earliest organic substances to be investigated, and their general chemical nature was elucidated, as long ago as 1811, by Chevreul.

All fats and fatty oils consist in the main of esters derived from the trihydric alcohol, glycerin,

$$CH_2(OH) . CH(OH) . CH_2 . OH,$$

and one or other of the higher monocarboxylic acids. The three most important of these esters or glycerides are glyceryl tripalmitate, or *palmitin*, glyceryl tristearate, or *stearin*, and glyceryl trioleate or *olein*. The formulæ of these compounds are as follows :—

Palmitin	Stearin	Olein
$CH_2 . O . CO . C_{15}H_{31}$	$CH_2 . O . CO . C_{17}H_{35}$	$CH_2 . O . CO . C_{17}H_{33}$
$CH . O . CO . C_{15}H_{31}$	$CH . O . CO . C_{17}H_{35}$	$CH . O . CO . C_{17}H_{33}$
$CH_2 . O . CO . C_{15}H_{31}$	$CH_2 . O . CO . C_{17}H_{35}$	$CH_2 . O . CO . C_{17}H_{33}$

A simple fat or oil, whether of vegetable or animal origin, is essentially a mixture of such glycerides in varying proportions. Palmitin and stearin are more or less hard, crystalline solids at ordinary temperatures ; olein and other unsaturated glycerides, on the other hand, are oily liquids. It is evident, therefore, that the consistency of a simple fat or oil will depend upon the relative proportions of liquid and solid glycerides. There is, in fact, no sharp distinction

between a fat and an oil. The difference is merely one of melting-point; and among natural products all gradations are known from the higher melting-point fats, such as mutton suet (melting-point, 45°-50°), to oils which remain liquid at temperatures well below 0°. Such substances as cocoanut oil and chaulmoogra oil are solid at ordinary temperatures in England, but are liquid in tropical countries. Other oils (for example, cotton-seed oil) become semi-solid in cold weather owing to the deposition of solid glycerides, and in such cases, the oil, if required for table use, is sometimes cooled and decanted or filtered from solid matter, thus yielding a so-called "winter oil" which remains clear even at low temperatures. When an oil is treated with hydrogen at fairly high temperatures in the presence of certain metallic catalysts, such as nickel, the unsaturated glycerides combine with the hydrogen, yielding saturated glycerides. This process is employed commercially for the conversion of oils into hard fats.

When boiled with solutions of sodium or potassium hydroxides, fats or oils become hydrolysed or "saponified" with formation of the sodium or potassium salts of the fatty acids (soaps) and free glycerin. The hydrolysis of stearin in this way may be represented as follows:—

$$\begin{array}{l} CH_2 . O . CO . C_{17}H_{35} \\ | \\ CH . O . CO . C_{17}H_{35} \\ | \\ CH_2 . O . CO . C_{17}H_{35} \end{array} + 3NaOH \rightarrow \begin{array}{l} CH_2 . OH \\ | \\ CH . OH \\ | \\ CH_2 . OH \end{array} + 3C_{17}H_{35} . COONa$$

Stearin — Glycerin — Sodium stearate

This process is used in the manufacture of soaps and of glycerin.

Saponification of olive oil.—Heat 50 grams of olive oil with 100 c.cs. of 20 per cent. caustic soda solution, on a sand bath, for half an hour, adding hot water from time to time to replace that lost by evaporation. On cooling, the soap (chiefly sodium oleate) solidifies on the surface as a hard cake. The separation of the soap will be more complete if it is "salted out" by addition of solid common salt before cooling.

Dissolve some of the soap in water and acidify with hydrochloric acid, when oleic acid separates as an oily layer.

Animal fats (e.g. prepared lard and prepared suet) are extracted from the minced fatty portions of animals by heating with water in lead-lined tanks. By this process the cells

of the tissues are burst, and molten fat separates on the surface as an oily layer, which can be drawn off.

Vegetable oils are commonly obtained from the fruit or comminuted seed by expression in hydraulic presses. The pressing may be carried out in the cold, or the crushed seed or meal may be previously heated in order to facilitate the flow of oil. Castor seeds, and other seeds containing large proportions of oil, are commonly treated by both methods, a preliminary cold pressing being followed by a hot one. " Cold-drawn " castor oil is that employed in medicine, the hot-drawn oil, which is more or less discoloured, being usually reserved for veterinary purposes.

Another method for obtaining vegetable oils is by extracting the crushed seed with volatile organic solvents, such as petroleum spirit, carbon disulphide, and carbon tetrachloride, which can be recovered by distillation after the extraction process. Solvent extraction is a more efficient process than expression, and is, in fact, commonly employed for the removal of the 10 per cent. or so of oil remaining in the " press cake " obtained in the expression process. On the other hand, oils obtained by solvent extraction are unsuitable for edible or medicinal purposes, since they invariably retain the flavour of the solvent.

Various processes are employed for the purification or refining of fats and oils. Foreign solid matter is separated by filtration or decantation, and free fatty acids are sometimes removed by shaking with aqueous caustic soda. In some cases steam is blown through the oil before filtration, in order to coagulate albuminous matter. Discoloured fats and oils are usually bleached by means of atmospheric oxygen or ozone, although chemical oxidising agents, such as potassium dichromate, are sometimes employed for this purpose.

Animal fats and oils.

The commonest animal fats employed in pharmacy are **prepared lard** and **prepared suet,** which are prepared from the crude fat of the pig and the sheep respectively by the process previously described. Both these substances consist almost entirely of palmitin, stearin, and olein, but whilst prepared lard contains about 50-60 per cent. of olein, prepared suet

contains only about 20-30 per cent. The result is that prepared lard is softer, and melts at a lower temperature than prepared suet. Mutton suet is employed for pharmaceutical purposes in preference to beef suet, on account of the fact that it contains rather less olein, and has, consequently, a higher melting-point.

Cod-liver oil for medicinal purposes is obtained by heating the fresh livers of cod-fish in steam-jacketed pans at a temperature of about 70°-80°. The liberated oil is drawn off and cooled to about — 5°, when a certain amount of solid fat (mostly stearin) separates, and is removed by filtration. The oil obtained in this way is pale yellow ; inferior qualities of oil, obtained from livers which have been allowed to putrefy, are darker in colour and more or less rancid, and are chiefly used in the manufacture of chamois leather.

In addition to the usual constituents of fats, cod-liver oil contains large proportions of the glycerides of jecoleic and therapic acids (*q.v.*). The nutritional properties of the oil have been attributed to these glycerides, but the value of the oil is now known to depend chiefly on the presence of fat-soluble vitamins A and D (see p. 147).

Vegetable fats and oils.

Oil of theobroma is an example of a solid vegetable fat. It consists principally of palmitin, stearin, and olein, together with small proportions of other glycerides.

Olive oil of the finest quality is obtained from ripe olives by cold expression. The oils obtained by hot expression, or by extracting the press cake with solvents, or from fermented fruit, are of inferior quality, and are usually employed in soap manufacture.

Olive oil contains about 70 per cent. of olein, the remainder consisting chiefly of palmitin, together with small quantities of arachin and other glycerides. When cooled to about 10°, the oil becomes semi-solid, owing to the separation of solid glycerides.

Olive oil is frequently adulterated with such relatively cheap substances as cotton-seed oil, arachis oil, and sesamé oil. Arachis oil, which contains considerable proportions (about 6 per cent.) of arachin, and sesamé oil, which contains

anything up to 20 per cent. of linolin, are used in some countries as substitutes for olive oil.

Detection of adulterants in olive oil.—The following tests may be applied to different samples of olive oil to which have been added about 20 per cent. of cotton-seed, arachis, and sesamé oils respectively.

Cotton-seed oil.—Mix 2 c.cs. of the adulterated oil with 1 c.c. of amyl alcohol and 1 c.c. of a 1 per cent. solution of precipitated sulphur in carbon disulphide. Warm on a water bath for about 30 minutes, when a red colour develops. This is known as the Halphen colour reaction, and is capable, under carefully regulated conditions, of detecting as little as 1 per cent. of cotton-seed oil in olive oil, although it should be noted that cotton-seed oil which has been previously heated to about 200° may fail to respond to the test. The nature of the red compound is unknown.

Arachis oil.—Saponify 1 c.c. of the adulterated oil by boiling with 15 c.cs. of N/1 alcoholic potash, under reflux, for 20 minutes. Set aside for 24 hours, warm on a water bath for 3 minutes, and set aside again for 24 hours, when crystals of crude potassium arachate separate.

Sesamé oil.—Shake 2 c.cs. of the oil with 1 c.c. of a freshly prepared 1 per cent. solution of sucrose in concentrated hydrochloric acid for half a minute. Allow to stand, and note the crimson colour of the acid layer. This, the Baudouin test, is an extremely delicate reaction, and is characteristic of sesamé oil.

Almond oil is obtained by expression from either sweet or bitter almonds, the two varieties of oil being almost identical in composition. Bitter almonds differ from sweet almonds in containing a cyanogenetic glucoside, amygdalin (p. 33), but this remains in the press cake after the expression process.

Almond oil consists mainly of olein. It is liable to adulteration with apricot and peach kernel oils, which are, in fact, sometimes substituted for it.

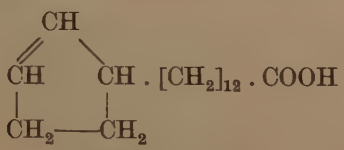
Detection of kernel oils (Bieber's test).—Shake 5 c.cs. of apricot or peach kernel oil vigorously with 1 c.c. of a cold, freshly prepared mixture of equal weights of concentrated sulphuric acid, fuming nitric acid and water. A pink or brown coloration is produced after some minutes.

This test is capable of distinguishing pure almond oil (which gives no colour) from the kernel oils, but cannot be relied upon for the detection of less than about 25 per cent. of the latter when present as adulterant.

Croton oil contains glycerides of a great variety of acids, but its cathartic action is apparently due to the presence of small quantities of a complex resin.

Chaulmoogra oil contains a cyclic unsaturated acid, chaulmoogric acid, $C_{17}H_{31}$. COOH, to which its bactericidal action is mainly due.

Chaulmoogric acid, which is present in the oil largely in the free state, has the following structure :—[1]



Chaulmoogric acid

Castor oil differs widely in composition from ordinary vegetable oils, in that it contains over 80 per cent. of the glycerides of ricinoleic and iso-ricinoleic acids, to which the purgative properties of the oil are probably due. Castor seeds contain an exceedingly poisonous substance, *ricin*, but this remains in the cake after expression of the oil.

Castor oil is strongly dextrorotatory, this property being doubtless due to the presence of an asymmetric carbon atom in ricinoleic acid.

Drying oils.

A large number of vegetable oils possess the property of absorbing atmospheric oxygen. Of these, the so-called semi-drying oils, such as sesamé oil and cotton-seed oil, become viscid on exposure to air, whilst the drying oils, such as linseed oil and poppy-seed oil, can absorb sufficient oxygen to become converted into elastic, translucent, amorphous solids. The peculiar properties of semi-drying and drying oils is attributable to the presence of glycerides of highly unsaturated acids, such as linolic and linolenic, which are readily oxidised by atmospheric oxygen with formation of amorphous solid products.

Linseed oil is obtained from crushed linseed by expression. It is a brownish, viscous liquid, which on exposure to air dries to a transparent, flexible solid known as *linoxyn*. The oil is employed in medicine and in the manufacture of paints, whilst linoxyn is used in making linoleum.

Boiled linseed oil is prepared by heating the oil with " driers," such as lead oxide, the drying properties of the oil being in this way enhanced.

[1] Barrowcliff and Power, *Trans. Chem. Soc.*, 1907, **91**, 557.

Chemical examination of fats and oils.

Different samples of a particular fat or oil may vary considerably in quality; further, the more expensive oils are frequently adulterated with cheaper varieties. The determination of the purity of a fat or oil is a matter of considerable difficulty, since all substances of this class are more or less complex mixtures. Evaluation is, to some extent, dependent upon the determination of such physical properties as melting-point, refractive index, and specific gravity. In addition, certain chemical values are of considerable importance in assessing the purity of a sample. The chief of these are the acid value, the saponification value, and the iodine value.

The acid value is the number of milligrams of potassium hydroxide required to neutralise the free fatty acids present in a gram of the fat or oil. Most pure fats and oils contain very little free acid, but on prolonged keeping, especially if they are impure, enzymes present may bring about partial decomposition, with separation of free fatty acids, the oil thus becoming rancid. The acid value is therefore a valuable test of freshness. Two examples of the importance of the acid value may be mentioned. Pure medicinal cod-liver oil should not contain more than a fraction of a per cent. of free fatty acids, whereas the so-called "natural oil" obtained from putrid cod livers may contain anything up to 50 per cent. Pure virgin olive oil, obtained by expression from the fresh fruit, contains about 0·5 per cent. of free fatty acids; whilst poorer quality oils, obtained from fruit which has been allowed to ferment, may contain as much as 30 per cent.

Those oils which contain considerable quantities of free acids as normal constituents will, of course, have normally high acid values (chaulmoogra oil, for example).

Determination of acid value.—Weigh out from 5 to 10 grams of the fat or oil, and mix in a flask with about 50 c.cs. of alcohol, which has been previously neutralised, if necessary, with potassium hydroxide. Heat the flask on a water bath until the fat has melted, and titrate slowly with N/10 potassium hydroxide, using phenolphthalein as indicator. The contents of the flask should be constantly shaken during the titration, and, at the end point, the pink colour should remain for at least a minute.

For the calculation, the number of milligrams of potassium hydroxide

used, divided by the weight (in grams) of fat or oil taken, gives the required acid value.

Example.—10 grams of fat required 21·0 c.cs. of N/10 KOH.
1000 c.cs. N/10 KOH contain 5600 milligrams of KOH.

$$\therefore \text{21·0 c.cs. KOH contain } 5600 \times \frac{21{\cdot}0}{1000} \text{ milligrams of KOH.}$$

$$= 117{\cdot}6 \text{ milligrams of KOH.}$$

$$\therefore \text{Acid value} = \frac{117{\cdot}6}{10} = 11{\cdot}76.$$

The saponification value represents the number of milligrams of potassium hydroxide required to completely saponify a gram of the fat or oil, and is determined by boiling with a known volume of standard alcoholic potassium hydroxide, and afterwards titrating back with standard hydrochloric acid. The saponification value varies slightly according to the relative proportions of the various glycerides present. Mineral oils contain no esters, and consequently have a zero saponification value; so that the saponification value is of importance in detecting the presence of mineral oil added as adulterant to such substances as linseed oil.

Determination of saponification value.—Prepare an approximately N/2 alcoholic solution of potassium hydroxide by dissolving about 30 grams of potassium hydroxide in the least possible quantity of water, diluting to 1000 c.cs. with alcohol and filtering through glass wool after standing for 24 hours.

Transfer a weighed quantity (1·5-2·0 grams) of the fat or oil to a 200 c.c. round-bottomed flask. Add 25 c.cs. of the alcoholic potassium hydroxide, and heat on a water bath, under reflux, for 30 minutes. At the same time, heat 25 c.cs. of the alcoholic potassium hydroxide under similar conditions, but without addition of the fat or oil. Cool both solutions and titrate them with N/2 hydrochloric acid, using phenolphthalein as indicator.

Example.—25 c.cs. of alcoholic KOH required 23·2 c.cs. of N/2 HCl.
25 c.cs. of alcoholic KOH plus 2 grams of fat required 9·2 c.cs. of N/2 HCl.
Hence, 2 grams of fat was equivalent to 23·2 − 9·2, or 14·0 c.cs. of N/2 KOH.

$$\text{14 c.cs. of N/2 KOH contain } \frac{28000 \times 14}{1000}, \text{ or 392 milligrams of KOH.}$$

$$\therefore \text{Saponification value of fat was } \frac{392}{2}, \text{ or 196.}$$

It should be noted that the saponification value actually represents the amount of potassium hydroxide required to saponify the glycerides, plus that used in neutralising the free fatty acids present.

The iodine value is perhaps the most important chemical constant of a fat or oil, and is of particular importance in the detection of adulterants. It represents the proportional

weight of iodine absorbed by 100 parts by weight of the fat or oil under certain fixed conditions. The absorption of iodine is due to direct addition to double bonds, and the iodine value therefore gives an indication of the proportion of unsaturated acids (oleic, linolic, linolenic, ricinoleic, etc.) in the substance. For this reason, solid fats have low iodine values (about 35-60); non-drying oils have iodine values of about 80-100; and drying oils have very high iodine values (up to 200).

Determination of iodine value.—For the determination of iodine values, a solution of iodine monochloride in glacial acetic acid (Wijs' solution) may be prepared by the following simplified process: 13 grams of iodine are dissolved in 1000 c.cs. of glacial acetic acid, and the solution is titrated with N/10 sodium thiosulphate. Chlorine, previously washed with water and dried by means of concentrated sulphuric acid, is then passed through the solution until the original titre is exactly doubled, thus marking the end point of the following reaction, which is also indicated by a fairly sharp change in colour :—

$$I_2 + Cl_2 = 2ICl.$$

Weigh out a suitable quantity of the substance to be examined (varying from about 0·15 gram in the case of drying oils to about 1·0 gram in the case of fats with low iodine values), transfer to a 1000 c.c. stoppered bottle, add about 10 c.cs. of carbon tetrachloride and shake until dissolved. Add 25 c.cs. of the iodine solution and keep in a dark place for 1 hour (or 2 hours in the case of oils with very high iodine values). Then add about 500 c.cs. of water and excess of potassium iodide, shake well, and titrate with N/10 sodium thiosulphate.

Carry out a blank experiment under identical conditions, but without addition of the fat or oil.

Example.—25 c.cs. of the iodine solution required 32·3 c.cs. N/10 thiosulphate.

1 gram of fat plus 25 c.cs. of the iodine solution required 16·3 c.cs. N/10 thiosulphate.

∴ 1 gram of fat absorbed iodine equivalent to 32·3 − 16·3 = 16·0 c.cs. N/10 thiosulphate.

This is equivalent to 16·0 × 0·0127 grams of iodine.

∴ Iodine value = 16·0 × 0·0127 × 100
= 20·3.

It should be noted that, in the above process, the fat or oil actually combines with chlorine as well as iodine, but the result is calculated as the equivalent weight of pure iodine.[1]

Waxes.

Waxes resemble fats and oils in composition, inasmuch as they consist largely of esters of the higher monocarboxylic

[1] See also Meigen and Winogradoff, *Zeit. angew. Chem.*, 1914, **27**, 241.

Substance.	Botanical or Zoological Source.	Melting-point.	Acid Value.	Saponification Value.	Iodine Value.[1]	Principal Constituents.
Almond oil	*Prunus Amygdalus* var. *amara* or *dulcis*	—	1·0-6·0	188-196	93-100	Olein.
Arachis oil	*Arachis hypogœa*	—	0·3-6·0	190-196	83-101	Arachin (6 %), stearin, olein, linolin.
Castor oil	*Ricinus communis*	—	0·4-4·0	177-187	83-90	Ricinolein, isoricinolein.
Chaulmoogra oil	*Taraktogenos Kurzii*	22°-30°	21-27	198-213	96-104	Palmitic acid, chaulmoogric acid and its homologues.
Cod-liver oil	*Gadus morrhua*	—	0·3-2·5	179-192	155-173	Jecolein, therapin, palmitin, stearin, vitamins.
Cotton-seed oil	Species of *Gossypium*	—	—	190-198	102-114	Palmitin, stearin, olein, linolin.
Croton oil	*Croton Tiglium*	—	—	210-215	102-106	Palmitin, stearin, laurin, myristin, croton resin.
Linseed oil	*Linum usitatissimum*	—	1·0-3·0	187-195	170-200	Palmitin, olein, linolin, linolenin.
Oil of Theobroma	*Theobroma Cacao*	30°-33°	1·0-2·0	188-195	35·5-37·5	Palmitin, stearin, olein.
Olive oil	*Olea europœa*	—	0·5-6·0	188-197	79-87	Palmitin, olein (70 %).
Prepared lard	*Sus scrofa*	35°-40°	Up to 1·2	192-198	52-63	Palmitin, stearin, olein (50-60 %).
„ suet	*Ovis aries*	45°-50°	Up to 2·0	192-195	33-46	Palmitin, stearin, olein (20-30 %).
Sesamé oil	*Sesamum indicum*	—	0·2-8·0	189-193	103-114	Olein, linolin (20 %).
Beeswax	*Apis mellifica*	61°-64°	17-21	87-99	8·8-10·7	Myricyl palmitate (80-90 %), cerotic acid.
Spermaceti	*Physeter macrocephalus*	43°-49°	0·1-1·0	125-136	3-4·4	Cetyl palmitate.
Wool fat	*Ovis aries*	36°-43°	0·6-1·8	83-102	10-28	Cholesterol, iso-cholesterol, and their esters.

[1] It is interesting to compare these iodine values with those of the commoner unsaturated acids: oleic acid, iodine value, 90·1; linolic acid, iodine value, 181·4; linolenic acid, iodine value, 274·1.

acids. But in this case the alcohol present in combination is not glycerin, but one or other of the higher monohydric alcohols, such as *cetyl alcohol*, $C_{16}H_{33}$. OH ; *ceryl alcohol*, $C_{26}H_{53}$. OH ; and *myricyl* or *melissyl alcohol*, $C_{30}H_{61}$. OH.

Most waxes are solids, and of animal origin. They are distinguishable from fats and oils by their low saponification and iodine values.

Yellow beeswax is made from the honeycomb of the bee by melting with water, separating from the aqueous layer, and straining from impurities, or by expression. It is a yellow solid, which retains to some extent the taste and odour of honey. The principal constituents are myricyl palmitate, $C_{15}H_{31}$. $COOC_{30}H_{61}$, and free cerotic acid, $C_{25}H_{51}$. COOH.

White beeswax is prepared by bleaching the yellow variety, either by exposure to air and sunlight, or by the action of chemical oxidising agents. Unlike yellow beeswax, it is colourless and odourless.

Spermaceti is a crystalline wax obtained by cooling the oil of the sperm whale. It consists principally of cetyl palmitate, $C_{15}H_{31}$. $COOC_{16}H_{33}$.

Wool fat is a waxy substance obtained from sheeps' wool, either by extraction with volatile organic solvents, or by emulsifying with soap solution, the emulsion being afterwards separated by addition of a mineral acid.

Wool fat is a complex waxy mixture, consisting largely of esters of *cholesterol* and *iso-cholesterol*. These substances are complex, unsaturated, monohydric alcohols, and are isomeric, both having the formula $C_{27}H_{45}$. OH. Cholesterol is present in small quantities in bile, and in most animal tissues.

Wool fat is capable of taking up a large proportion of water to form a thick cream, known as hydrous wool fat or "lanolin". It is used as a base in the preparation of ointments in which large proportions of liquids are to be incorporated.

CHAPTER IV.

CARBOHYDRATES.

VEGETABLE drugs consist largely of carbohydrates, such as sugars, starches, and celluloses. These substances are composed of carbon, hydrogen, and oxygen, the last two elements being usually present in the proportions in which they occur in water.

The reactions by which carbohydrates are built up in a plant are not completely understood. The synthesis of a simple sugar, from carbon dioxide and water, takes place in the green parts of the plant under the influence of light and chlorophyll. From this sugar more complex carbohydrates are built up within the protoplasm, some of these being secreted in the form of celluloses to produce new cell walls. During the day, when photosynthesis is actively taking place, part of the carbohydrate content is stored in the leaves in the form of small starch granules. At night this starch is hydrolysed by enzyme action into sugars, which then pass to other parts of the plant.

Many plants form food reserves of carbohydrates, such as starch and inulin, in their underground organs. Starch, which is insoluble, is produced by the action of colourless protoplasmic bodies known as leucoplasts from sugars conveyed from the leaves, while inulin is itself soluble in the cell sap. When these reserves are required by the plant they are hydrolysed to soluble sugars by means of enzymes, such as diastase and inulase.

Animals, unlike plants, are unable to carry out photosynthesis, and must derive their carbohydrates from plants. Such carbohydrates, if not present in the food as soluble sugars, are hydrolysed by enzymes, such as ptyalin present in the saliva and the amylase of the pancreatic juice. Carbohydrate reserves are stored in animals as in plants. Animal

starch or glycogen is synthesised from glucose and stored in the tissues, chiefly in the liver and muscles ; when required for use it is reconverted into glucose.

The carbohydrates may be conveniently classified as follows :—

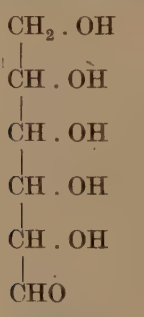
(*a*) Monosaccharides
(*b*) Disaccharides
(*c*) Trisaccharides } sugars.
(*d*) Tetrasaccharides
(*e*) Polysaccharides (starches and celluloses).

Monosaccharides.

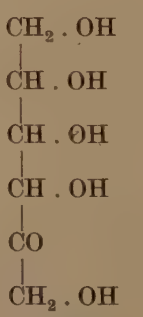
The monosaccharides are the simplest sugars, and differ from the other carbohydrates in that they cannot be hydrolysed. Monosaccharides are, in fact, the final products of hydrolysis of all the more complex carbohydrates.

The commonest monosaccharides are isomeric compounds of the formula $C_6H_{12}O_6$, and are known as *hexoses*. Other and less common monosaccharides are the *tetroses*, $C_4H_8O_4$, and the *pentoses*, $C_5H_{10}O_5$.

The monosaccharides were, until recently, regarded as aldehydes or ketones derived from polyhydric alcohols ; thus the two commonest hexoses, glucose and fructose, were represented by the following formulæ :—



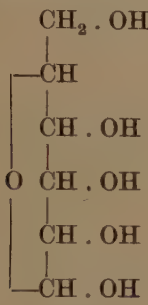
Glucose



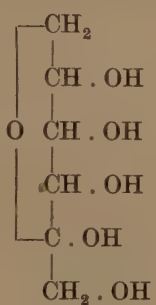
Fructose

Whilst such formulæ may usefully summarise the simpler properties of the sugars, more recent work has led to the conclusion that the monosaccharides, in their stable forms,

have cyclic oxide structures, and they are now usually represented by such formulæ as :—



Glucose [1]



Fructose [2]

The monosaccharides, on reduction, yield the corresponding polyhydric alcohols, some of which occur naturally. Thus the hexahydric alcohol, *mannitol*,

$$CH_2(OH) . CH(OH) . CH(OH) . CH(OH) . CH(OH) . CH_2 . OH,$$

which is the reduction product of the hexose mannose, is of fairly common occurrence in plants, and constitutes about 40-60 per cent. of the manna obtained from the manna ash, and 90 per cent. of eucalyptus manna. The isomeric hexahydric alcohol *dulcitol* occurs in considerable quantities in euonymus bark.

Arabinose, $C_5H_{10}O_5$, is a pentose which is formed by the hydrolysis of acacia and other gums.

Rhamnose, $CH_3 . C_5H_9O_5$, is a methyl pentose which occurs in combination in certain glucosides and gluco-resins. An isomeric methyl pentose, *fucosan*, is a constituent of several sea-weeds, such as Irish moss.

Glucose, $C_6H_{12}O_6$, sometimes known as dextrose (on account of the fact that it is dextrorotatory), is the most important of the monosaccharides, and is usually prepared by hydrolysing starch with boiling dilute sulphuric acid. It is an important constituent of prunes, figs, and raisins.

Pure glucose is a white crystalline powder, but the substance used in medicine is a viscous syrup, containing about 20 per cent. of water, with considerable proportions of maltose and dextrin.

[1] Charlton, Haworth, and Peat, *Trans. Chem. Soc.*, 1926, **128,** 89.
[2] Haworth and Hirst, *Trans. Chem. Soc.*, 1926, **128,** 1858.

Glucose, like all other carbohydrates, chars readily when heated alone or with concentrated sulphuric acid. Like many of the sugars, it is a powerful reducing agent, and precipitates gold and silver from solutions of their salts.

Tests for glucose.—1. Warm glucose with concentrated sulphuric acid, and observe that it chars, though not so readily as cane sugar.

2. Prepare an ammoniacal solution of silver hydroxide by adding very dilute ammonia to silver nitrate solution, drop by drop, until the precipitate first formed just redissolves. Add a little glucose and warm gently in a clean test-tube, when metallic silver will be deposited on the sides of the tube as a mirror.

3. *Fehling's solution*, an alkaline cupric solution widely employed for the detection and estimation of reducing sugars, is prepared as follows :—

No. 1 Solution :	Crystalline copper sulphate,	34·64 grams.
	Sulphuric acid,	0·5 c.c.
	Water to	500 c.cs.
No. 2 Solution :	Sodium potassium tartrate,	176 grams.
	Sodium hydroxide,	77 ,,
	Water to	500 c.cs.

Equal volumes of the two solutions are mixed immediately before use.

Warm some Fehling's solution with glucose, when the cupric solution is reduced, with precipitation of red cuprous oxide, Cu_2O.

Fructose, $C_6H_{12}O_6$, is isomeric with glucose, from which it differs in being lævorotatory (hence the name lævulose, by which it is sometimes known). It is present in many fruits, and, as a constituent of invert sugar (*q.v.*), in honey.

Disaccharides.

The disaccharides have the molecular formula $C_{12}H_{22}O_{11}$. A disaccharide molecule is derived theoretically from two hexose molecules, which may be either identical or different, by condensation with elimination of a molecule of water. This is evident from the fact that disaccharides can be hydrolysed by water, in the presence of a mineral acid or an enzyme, with formation of either one or two hexoses :—

$$\underset{\text{Disaccharide}}{C_6H_{11}O_5 \cdot O \cdot C_6H_{11}O_5} + H_2O = \underset{\text{Hexose}}{C_6H_{12}O_6} + \underset{\text{Hexose}}{C_6H_{12}O_6}$$

Sucrose is the disaccharide obtained from the sugar cane or sugar beet. On hydrolysis with mineral acids or by the action of the enzyme invertase, sucrose is converted into a mixture of equal proportions of glucose and fructose, the

mixture being known as " invert sugar " (owing to the fact that it is slightly lævorotatory, whereas sucrose is dextrorotatory) :—

$$\underset{\text{Sucrose}}{C_{12}H_{22}O_{11}} + H_2O = \underset{\text{Glucose}}{C_6H_{12}O_6} + \underset{\text{Fructose}}{C_6H_{12}O_6}$$

Inversion of sucrose.—Dissolve about 1 gram of cane sugar in 10 c.cs. of water. Boil the solution with an equal volume of dilute hydrochloric acid for 5 minutes, and then add sodium hydroxide till just alkaline. Test this solution for invert sugar by adding Fehling's solution and heating to boiling, when red cuprous oxide is precipitated. Test the original cane sugar with Fehling's solution and note the difference.

Honey consists largely of invert sugar ; ripe juniper berries contain about 33 per cent., and tamarind pulp about 25-40 per cent.

Maltose is a disaccharide found in germinating seeds, where it is produced by the action of the enzyme diastase on starch. On hydrolysis it yields glucose only :—

$$\underset{\text{Maltose}}{C_{12}H_{22}O_{11}} + H_2O = 2\underset{\text{Glucose}}{C_6H_{12}O_6}$$

Lactose is a disaccharide occurring in the milk of mammals. It may be obtained from milk by adding rennet in order to precipitate the casein in curds, filtering, and evaporating the clear filtrate to crystallisation. Lactose, on hydrolysis, yields the two hexoses, glucose and galactose :—

$$\underset{\text{Lactose}}{C_{12}H_{22}O_{11}} + H_2O = \underset{\text{Glucose}}{C_6H_{12}O_6} + \underset{\text{Galactose}}{C_6H_{12}O_6}$$

Tri- and Tetrasaccharides.

The trisaccharides, $C_{18}H_{32}O_{16}$, and the tetrasaccharides, $C_{24}H_{42}O_{21}$, are derived theoretically from three and four hexose molecules respectively.

Gentianose is a trisaccharide present, together with sucrose, in fresh gentian root. It can be hydrolysed to a mixture of glucose and fructose, the hydrolysis taking place in two stages, the first of which involves the formation of a disaccharide, *gentiobiose* :—

$$\underset{\text{Gentianose}}{C_{18}H_{32}O_{16}} + H_2O = \underset{\text{Gentiobiose}}{C_{12}H_{22}O_{11}} + \underset{\text{Fructose}}{C_6H_{12}O_6}$$

$$\underset{\text{Gentiobiose}}{C_{12}H_{22}O_{11}} + H_2O = 2\underset{\text{Glucose}}{C_6H_{12}O_6}$$

During the drying of gentian root, enzymes present bring about the hydrolysis of the sucrose and gentianose, with formation of a mixture of glucose, fructose, and gentiobiose.

Mannotriose and **mannotetrose** are tri- and tetrasaccharides which occur in the manna obtained from the manna ash. On hydrolysis they yield mixtures of hexoses :—

$$\underset{\text{Mannotriose}}{C_{18}H_{32}O_{16}} + 2H_2O = \underset{\text{Glucose}}{C_6H_{12}O_6} + \underset{\text{Galactose}}{2C_6H_{12}O_6}$$

$$\underset{\text{Mannotetrose}}{C_{24}H_{42}O_{21}} + 3H_2O = \underset{\text{Glucose}}{C_6H_{12}O_6} + \underset{\text{Fructose}}{C_6H_{12}O_6} + \underset{\text{Galactose}}{2C_6H_{12}O_6}$$

Eucalyptus manna contains a trisaccharide, *raffinose*, which on hydrolysis yields a mixture of glucose, fructose, and galactose.

Polysaccharides.

The polysaccharides are exceedingly complex substances of high molecular weight, which have the approximate empirical formula $C_6H_{10}O_5$. On hydrolysis, they become split up, with formation of sugars.

Starch is found principally in the roots, rhizomes, and seeds of plants. Medicinal starch is usually obtained from wheat, maize, or rice ; maranta starch is used under the name of arrowroot ; tapioca and sago consist respectively of the partly gelatinised starches of cassava and of various species of palm. Cheap starches, particularly potato starch, are used in the production of alcohol.

Crude starch consists of granules which appear to be built up in concentric layers, and starches from different sources may be distinguished microscopically by the differences in the size, shape, and striations of the granules. When starch is boiled with water, the granules swell up and burst, and, on cooling, the mixture sets to an opalescent jelly. Starch is coloured deep blue by iodine, owing to the formation of a loose compound—" starch iodide."

Diastatic hydrolysis converts starch into maltose, and a certain amount of a polysaccharide known as dextrin, both of which, on further hydrolysis, yield glucose. The complete hydrolysis of starch to glucose may be brought about by prolonged boiling with dilute mineral acids :—

$$\underset{\text{Starch}}{(C_6H_{10}O_5)n} + nH_2O = \underset{\text{Glucose}}{nC_6H_{12}O_6}.$$

Detection of starch.—Add a few drops of dilute iodine solution to some cold starch mucilage, and observe the blue colour. Note that the colour disappears on warming and returns on cooling.

Boil a little starch mucilage with dilute hydrochloric acid for 5 minutes, make alkaline with sodium hydroxide, and show the presence of glucose by means of Fehling's solution. Note that starch mucilage itself does not reduce Fehling's solution.

Action of diastase on starch.—Dilute about 2 grams of malt extract with 100 c.cs. of cold water, and filter. Place 5 c.cs. of starch solution in each of two test tubes. Add to one 5 c.cs. of the diluted malt extract (which contains diastase), and to the other, 5 c.cs. of the diluted extract which has been previously boiled in order to destroy the activity of the enzyme. Place the tubes in a water bath at 50°, and test the liquids at intervals for starch by adding a drop of the solution to a drop of dilute iodine solution on a tile. Note that, after a time, the solution containing the unboiled malt extract ceases to give a blue colour. Finally, add Fehling's solution to each tube, heat to boiling, and note the result.

Inulin is a polysaccharide which replaces starch as a food reserve in many plants of the natural orders *Compositæ* and *Campanulaceæ*, notably elecampane root (20-45 per cent.), pellitory root (50 per cent.), arnica rhizome, and dandelion root.

Inulin is a white, amorphous or crystalline powder, and yields fructose on hydrolysis. It may be distinguished from starch by the fact that it dissolves in water at about 70° without gelatinising, and that it gives only a pale yellowish colour with iodine. Inulin is, like starch, insoluble in alcohol, and is precipitated by addition of alcohol to its aqueous solution.

Distinction of inulin from starch.—Note the solubility in hot water, and the fact that the cooled solution does not give a blue colour with iodine.

Lichenin and *iso-lichenin* are polysaccharides which occur in many lichens, and are the main constituents of Iceland moss. On hydrolysis they yield glucose.

Gelose, the principal constituent of agar-agar, is a polysaccharide which, on hydrolysis, yields the hexose galactose.

Carrageenin is the name which has been given to a mixture of carbohydrates constituting about 63 per cent. of Irish moss. On hydrolysis, it yields a mixture containing glucose, fructose, and galactose.

Glycogen is an amorphous, starchy substance found in the livers and other parts of animals.

Glycogen is almost entirely soluble in water. Diastatic

hydrolysis converts it into maltose, and, on complete hydrolysis with enzymes or dilute mineral acids, it yields glucose. It differs from vegetable starches in that it gives with iodine a characteristic red or reddish-brown colour.

Cellulose and similar substances form the framework of all vegetable tissues, but, although they occur in considerable quantities in most vegetable drugs, they are not of any particular medicinal importance.

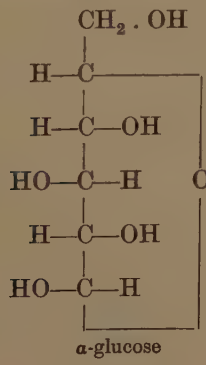
CHAPTER V.

GLUCOSIDES.

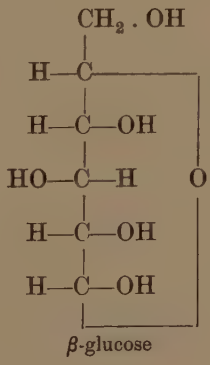
The term glucoside embraces substances of the most varying and diverse character, some of which are exceedingly complex in composition, whilst others are relatively simple. They derive their general name from the fact that, on hydrolysis by water under the influence of enzymes or mineral acids, they yield a sugar (usually glucose) together with some other compound or compounds. The product of hydrolysis of a glucoside other than a sugar is usually some kind of hydroxy organic compound, such as an alcohol, a phenol, or a hydroxy acid.

Those glucosides which do not yield glucose on hydrolysis are sometimes distinguished by class names which indicate the sugar from which they are derived. Thus, glucosides which yield rhamnose on hydrolysis are sometimes spoken of as *rhamnosides*.

An aqueous solution of ordinary glucose contains an equilibrium mixture of two stereoisomerides, α-glucose and β-glucose, which differ in optical rotation, and may be represented by the two following configurational modifications of the structural formula :—

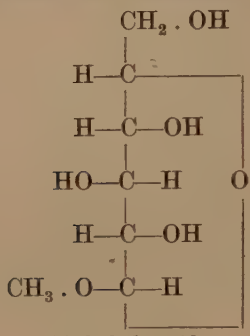


α-glucose

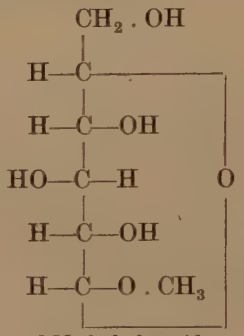


β-glucose

The simplest glucosides are the alkyl glucosides, which do not occur in nature, but have been made synthetically. Thus, methyl glucoside is formed by the interaction of glucose and methyl alcohol in the presence of hydrochloric acid. The product is really a mixture of two stereoisomerides, *α-methyl glucoside* and *β-methyl glucoside*, which are formed respectively from α-glucose and β-glucose :—



α-Methyl glucoside



β-Methyl glucoside

The mixture can be separated into its two components by fractional crystallisation, or by the action of certain organisms.

The alkyl glucosides are colourless, crystalline compounds. They can be hydrolysed by boiling with dilute mineral acids, with formation of glucose and the corresponding alcohol. This hydrolysis can also be brought about by the action of certain enzymes, notably emulsin (a naturally occurring mixture of enzymes) and maltase. It is an interesting fact that emulsin can bring about the hydrolysis only of β-glucosides (such as β-methyl glucoside), whilst maltase is capable only of hydrolysing the stereoisomeric α-glucosides (such as α-methyl glucoside).

Preparation of emulsin.—A solution of emulsin may be conveniently prepared from sweet almonds. Blanch and powder the almonds, infuse in cold water, and strain. To each 100 c.cs. of infusion add two or three drops of glacial acetic acid to precipitate proteins. Filter, and add an equal volume of alcohol. The precipitate of crude emulsin is collected on a filter, washed with alcohol, and dissolved in water.

This solution may be used to bring about the hydrolysis of salicin, as described later.

The naturally occurring glucosides are usually colourless, crystalline substances, soluble in water or dilute alcohol, and

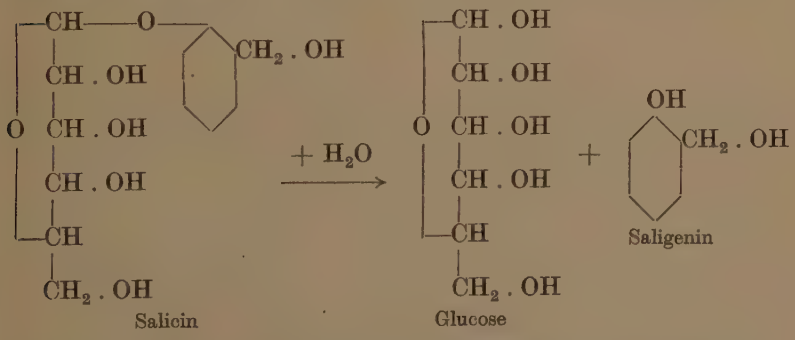
having a bitter taste. They are usually similar in structure to the alkyl glucosides, except that they contain more complex groups in place of the simple alkyl radicle.

Like the alkyl glucosides, naturally occurring glucosides can be hydrolysed by water in the presence of mineral acids or enzymes, and they have been divided into two classes, corresponding respectively in type to α-methyl glucoside and β-methyl glucoside, according as to whether they can be hydrolysed by maltase or emulsin. The great majority of natural glucosides are of the β-type.

In plants, glucosides are usually accompanied by enzymes capable of bringing about their hydrolysis, the glucosides and enzymes being contained in separate cells. If the cells of such a plant are ruptured in presence of water, the glucosides may be brought into contact with the enzymes, and so become hydrolysed. For this reason glucosides originally present in a plant will not necessarily be found in the drug or in galenicals prepared from it. Hydrolysis of glucosidal matter in this way is often desirable, but, if it is not, it can sometimes be prevented by processes of stabilisation, as mentioned in the introductory chapter.

Salicin, $C_6H_{11}O_5 . O . C_6H_4 . CH_2 . OH$, occurs in various species of *Salix* and of *Populus*. It is usually prepared from *S. fragilis* or *S. purpurea*.

Salicin is a colourless, crystalline compound, soluble in water, and having an intensely bitter taste. On hydrolysis by dilute acids or emulsin, it yields glucose and salicyl alcohol (saligenin) :—



If salicin is warmed with potassium dichromate and dilute sulphuric acid, the saligenin first produced is oxidised to

salicylaldehyde, which may be recognised by its characteristic odour.

Tests for salicin.—1. To a little salicin on a white tile add a drop of concentrated sulphuric acid, and note the red coloration.

2. Boil salicin with dilute sulphuric acid and potassium dichromate, and note the odour of salicylaldehyde.

3. Hydrolyse some salicin by boiling with dilute sulphuric acid in a small flask for about 15 minutes. Neutralise the liquid with sodium hydroxide, and test for glucose with Fehling's solution.

4. Salicin may also be hydrolysed by means of emulsin, as follows: To 5 c.cs. of a 2 per cent. solution of salicin add an equal volume of emulsin solution, prepared as previously described (p. 30). Warm on a water bath at 40° for 15 minutes, and then test for glucose with Fehling's solution.

Some species of *Populus* contain, in addition to salicin, the glucoside *populin*, which is benzoyl salicin. Hydrolysis of populin, by an enzyme present in the plant, yields salicin and benzoic acid.

Arbutin, $C_6H_{11}O_5 . O . C_6H_4 . OH$, is one of the simplest natural glucosides, and is found in many Ericaceous plants, such as the bearberry. It is a colourless, crystalline compound, soluble in hot water, from which it separates, on cooling, in colourless needles. Like most glucosides, it has a bitter taste. On hydrolysis by dilute mineral acids or emulsin, it yields glucose and quinol (hydroquinone) :—

$$\underset{\text{Arbutin}}{C_6H_{11}O_5 . O . C_6H_4 . OH} + H_2O = \underset{\text{Glucose}}{C_6H_{12}O_6} + \underset{\text{Quinol}}{C_6H_4(OH)_2}.$$

Gaultherin, $C_6H_{11}O_5 . O . C_6H_4 . COOCH_3$, is a glucoside which occurs in wintergreen leaves. On crushing the leaves with water, the glucoside becomes hydrolysed by an enzyme, gaultherase, yielding glucose and methyl salicylate (oil of wintergreen) :—

$$\underset{\text{Gaultherin}}{C_6H_{11}O_5 . O . C_6H_4 . COOCH_3} + H_2O = \underset{\text{Glucose}}{C_6H_{12}O_6} + \underset{\text{Methyl salicylate}}{C_6H_4(OH) . COOCH_3}.$$

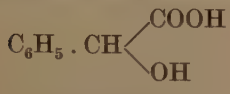
The bark of *Betula lenta* contains a glucoside which yields methyl salicylate on hydrolysis, but this glucoside is probably not identical with gaultherin.

Cyanogenetic glucosides.

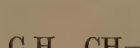
Cyanogenetic glucosides are an important class of natural substances which yield hydrocyanic acid as one of the pro-

ducts of their hydrolysis. They are of common occurrence in plants, particularly those of the natural order *Rosaceæ*.

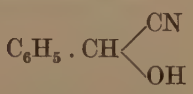
The common cyanogenetic glucosides are derivatives of mandelo-nitrile, which may be regarded as the nitrile of mandelic acid or as the cyanohydrin of benzaldehyde :—



Mandelic acid

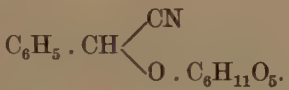


Benzaldehyde

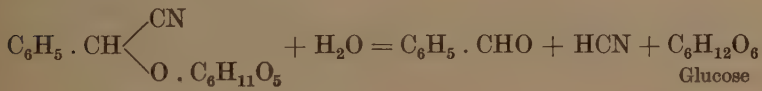


Mandelo-nitrile
(benzaldehyde cyanohydrin)

Mandelo-nitrile contains an asymmetric carbon atom, and can, therefore, exist in *d*- and *l*- forms, and as a *dl*- mixture. Three simple stereoisomeric glucosides—sambunigrin, prunasin, and prulaurasin—are derived from one molecule of glucose and one of *d*-, *l*-, or *dl*-mandelo-nitrile. They all have the structural formula—



Prulaurasin, or *dl*-mandelo-nitrile glucoside, occurs in cherry-laurel leaves, together with the enzyme prunase, which, when the leaves are crushed and macerated with water, hydrolyses the glucoside to benzaldehyde, hydrocyanic acid, and glucose :—



Prulaurasin

Glucose

Prunasin, or *l*-mandelo-nitrile glucoside,[1] occurs, together with prunase, in wild cherry bark. It differs from prulaurasin in physical properties and in optical rotation, but yields the same products when hydrolysed by prunase.

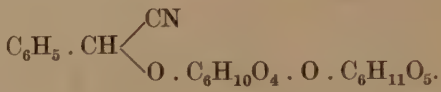
Sambunigrin, or *d*-mandelo-nitrile glucoside, is the cyanogenetic glucoside of the elder.

Amygdalin, $C_{20}H_{27}O_{11}N$, $3H_2O$, occurs in bitter almonds, and is present in the press-cake, remaining after expression

[1] By "*l*-mandelo-nitrile" is meant the nitrile which yields lævorotatory mandelic acid on hydrolysis. Some confusion exists as to the nomenclature of these compounds.

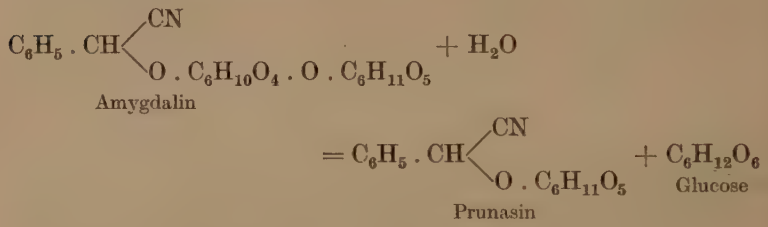
of the fatty oil. It is a bitter, crystalline powder, readily soluble in water.

Amygdalin has been made synthetically,[1] and is known to be a condensation product of *l*-mandelo-nitrile and gentiobiose (p. 25). The structural formula of amygdalin is, therefore,

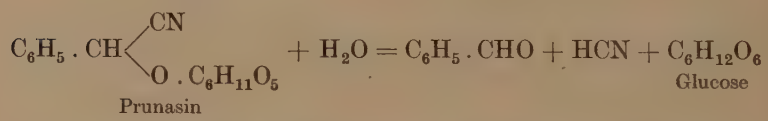


Bitter almonds also contain, in separate cells, the mixture of enzymes emulsin. When the seeds are crushed with water and allowed to stand, the enzymes amygdalase and prunase present in the emulsin bring about the hydrolysis of the amygdalin in two stages :—

Action of amygdalase :—



Action of prunase :—



The hydrolysis of amygdalin by mineral acids may follow a number of different courses.[2] With fairly concentrated sulphuric acid, the products are glucose (2 molecules) and *l*-mandelo-nitrile. Concentrated hydrochloric acid first hydrolyses the —CN group of amygdalin to —COOH, the final products being glucose (2 molecules), *l*-mandelic acid, and ammonia. With dilute hydrochloric acid the hydrolysis of amygdalin follows the same course as with emulsin.

[1] Campbell and Haworth, *Trans. Chem. Soc.*, 1924, **125,** 1337 ; Kuhn and Sobotka, *Ber.*, 1924, **57** (B), 1767.

[2] Walker and Krieble, *Trans. Chem. Soc.*, 1909, **95,** 1369.

Sweet almonds contain emulsin, but no amygdalin, and they do not, therefore, yield any hydrocyanic acid when crushed and macerated with water.

Iso-thiocyanate glucosides.

Many plants of the natural order *Cruciferæ* contain glucosides which, on hydrolysis, yield esters of iso-thiocyanic acid, H . N : C : S. The allyl, acrinyl, crotonyl, iso-butyl, benzyl, and phenylethyl esters have all been isolated as products of hydrolysis of various natural glucosides.

Sinigrin, $C_3H_5 . N : C(SO_4K) . S . C_6H_{11}O_5, H_2O$, the best known of the iso-thiocyanate glucosides, is present in black mustard seeds. Contained in separate cells is the enzyme *myrosin*, which, when the seeds are crushed and moistened, brings about the hydrolysis of the glucoside, with formation of allyl iso-thiocyanate, potassium hydrogen sulphate, and glucose, according to the following equation :—[1]

$$\underset{\text{Sinigrin}}{C_3H_5 . N : C(SO_4K) . S . C_6H_{11}O_5} + H_2O = C_3H_5 . N : C : S + KHSO_4 + C_6H_{12}O_6.$$

It is to the presence of free allyl iso-thiocyanate, which is a volatile liquid, that the crushed and moistened seeds owe their pungent odour and taste.

Sinigrin and myrosin are also present in fresh horse-radish root.

Sinalbin, $C_{30}H_{42}O_{15}N_2S_2$, is a glucoside which occurs in white mustard seeds, together with the enzyme myrosin. On crushing the seeds with water, the sinalbin is hydrolysed to acrinyl iso-thiocyanate, sinapin hydrogen sulphate, and glucose :—

$$\underset{\text{Sinalbin}}{C_{30}H_{42}O_{15}N_2S_2} + H_2O = \underset{\substack{\text{Acrinyl}\\ \text{iso-thiocyanate}}}{C_7H_7O . N : C : S} + \underset{\substack{\text{Sinapin}\\ \text{hydrogen}\\ \text{sulphate}}}{C_{16}H_{24}O_5N . HSO_4} + \underset{\text{Glucose}}{C_6H_{12}O_6}$$

Acrinyl iso-thiocyanate is a liquid with a pungent taste, but, unlike allyl iso-thiocyanate, it is not very volatile. For this

[1] Wrede, Banik, and Brauss, *Z. physiol. Chem.*, 1923, **126,** 210.

reason, white mustard seeds do not yield, when crushed, the pungent odour characteristic of black mustard seeds.

Saponins.

Saponins are glucosidal substances which occur in plants of a number of natural orders, especially *Rosaceæ*, *Caryophyllaceæ*, and *Sapindaceæ*. They are usually water-soluble, and derive their general name from the fact that they form soap-like froths when shaken with water. Many saponins are capable of destroying red blood corpuscles, and are, for this reason, exceedingly toxic when introduced into the blood stream. Even in very dilute solution they stupefy cold-blooded animals, and many of them cause sneezing.

Some saponins have feeble acidic properties, whilst others are neutral. On hydrolysis, they yield substances called *sapogenins*, which are usually insoluble in water, together with sugars such as arabinose, glucose, and galactose. Sapogenins are usually non-poisonous, and many of them appear to be related to the terpenes (p. 95), since they yield terpene hydrocarbons on distillation over zinc dust.

The hydrolysis of saponins is readily brought about by dilute acids, and this may explain the fact that saponins are much less toxic when taken by the mouth than when they are intravenously injected.

Detection of saponins.—1. Note the soap-like froth produced when tincture of quillaja is shaken with water.

2. Add concentrated sulphuric acid to tincture of quillaja, and note the deep brownish-red coloration.

Quillaja saponins.—Commercial " saponin " is obtained from quillaja bark by extraction with boiling water. It contains an acid saponin (quillajic acid) and a neutral and more poisonous saponin (quillaja sapotoxin).[1]

When a solution of commercial " saponin " is boiled with dilute hydrochloric acid, the saponins become hydrolysed with formation of the corresponding sapogenins, which, being insoluble in water, are precipitated. In a simple form the hydrolysis may be expressed as follows :—

[1] There has been little recent work on the chemistry of the quillaja saponins. The literature is summarised by Cofman-Nicoresti and Tallantyre, *Y.B. Pharm.*, 1923, 726.

$$\underset{\text{Quillajic acid}}{2C_{19}H_{30}O_{10}} + 8H_2O = \underset{\text{Glucose}}{4C_6H_{12}O_6} + \underset{\text{Quillajic sapogenin}}{C_{14}H_{22}O_4}$$

$$\underset{\text{Quillaja sapotoxin}}{2C_{17}H_{26}O_{10}} + 7H_2O = \underset{\text{Glucose}}{4C_6H_{12}O_6} + \underset{\text{Quillaja sapotoxin sapogenin}}{C_{10}H_{18}O_3}$$

In actual fact, small quantities of other sugars, such as galactose, are produced in addition to the glucose, doubtless owing to the presence of glucosidal substances other than quillajic acid and quillaja sapotoxin.

Senega saponins.—Senega root contains an acid saponin (polygalic acid) and a neutral saponin (senegin). These closely resemble the saponins of quillaja bark. On hydrolysis, senegin is converted into a crystalline sapogenin, *senegenin*, $C_{26}H_{44}O_6$.[1]

Sarsaparilla saponins.—From Jamaica sarsaparilla root, a definite crystalline glucoside, *sarsasaponin*, $C_{44}H_{76}O_{20}$, $7H_2O$, has been isolated.[2] This, on hydrolysis, yields *sarsasapogenin*, $C_{26}H_{42}O_3$, and glucose :—

$$\underset{\text{Sarsasaponin}}{C_{44}H_{76}O_{20}} + H_2O = \underset{\text{Sarsasapogenin}}{C_{26}H_{42}O_3} + \underset{\text{Glucose}}{3C_6H_{12}O_6}.$$

Sarsasapogenin yields a terpene hydrocarbon, $C_{10}H_{16}$, on distillation over zinc dust.[3]

Honduras sarsaparilla root apparently contains a mixture of saponins, which yield sarsasapogenin and various sugars on hydrolysis.[4] It is probable that the saponin or saponins originally present in the root undergo partial decomposition on keeping.

Guaiacum saponins.—Guaiacum wood contains two non-toxic saponins, guaiacsaponic acid and guaiacsaponin, but these are of little medicinal importance.

Strophanthus glucosides.

The seeds of different species of *Strophanthus* contain different but closely related glucosides, which are known

[1] Wedekind and Krecke, *Ber.*, 1924, **57** (B), 1118.
[2] Power and Salway, *Trans. Chem. Soc.*, 1914, **105**, 201.
[3] Kaufmann and Fuchs, *Ber.*, 1923, **56** (B), 2527.
[4] *Ibid., loc. cit.*

collectively as strophanthins. These are most conveniently distinguished from one another by the use of the initial letter of the species ; thus the active principle of the seeds of *Strophanthus Kombé* is referred to as *k*-strophanthin.

Different samples of the strophanthin obtained from any particular species often vary considerably in melting-point and in ultimate composition, and it is doubtful whether these glucosides have yet been obtained in the pure state.

k-Strophanthin, sometimes known simply as strophanthin, is a white crystalline powder, freely soluble in water. It yields, on hydrolysis with dilute acids, a complex unsaturated alcohol, *strophanthidin*, $C_{23}H_{32}O_6$.[1] *k*-Strophanthin has recently been definitely proved to be a mixture, and from it has been isolated what is apparently a pure crystalline glucoside derived from strophanthidin and a disaccharide.[2]

k-Strophanthin and *h*-strophanthin (from *S. hispidus*) both give green colorations with cold 80 per cent. sulphuric acid. This reaction serves as a test for distinguishing seeds of the above two varieties from those of *S. Courmontii*, *S. Nicholsoni*, *S. gratus*, and *S. Emini*, all of which give red colorations under similar conditions.

Test for strophanthus seeds.—The sulphuric acid test for strophanthus as usually carried out is not very reliable, and the following modification is recommended.[3]

Crush three or four seeds in a porcelain dish with 1 c.c. of water (or better, alcohol). Dip a piece of filter paper first in this liquid and then in concentrated sulphuric acid, drain, and place in a clean, dry dish. Slowly dry the paper by gently warming the dish, when the characteristic green or red colour is developed, according to the variety of seeds tested.

g-Strophanthin (from *S. gratus*) is commonly known as *ouabain*. It is put on the market as a crystalline powder, and is used as a standard in the biochemical assay of strophanthus and digitalis and their preparations.

Digitalis glucosides.

The literature dealing with the digitalis glucosides is voluminous and confusing, and frequently contradictory.

[1] See Jacobs and others, *J. Biol. Chem.*, 1922, **54,** 253 ; 1923, **57,** 553 and 569 ; 1924, **59,** 713 ; 1924, **61,** 387 ; 1925, **63,** 123.

[2] Jacobs and Hoffmann, *J. Biol. Chem.*, 1926, **67,** 609.

[3] Mattei, *Arch. farm. sper.*, 1924, **38,** 76.

A number of glucosides have been described as occurring in the leaves or seeds of *Digitalis purpurea*, but some of these have been proved to be mixtures, whilst others have only been obtained in a state of doubtful purity. The subject is complicated by the fact that the same name has been sometimes applied by different investigators to entirely different substances.

In their constituents, the leaves and seeds differ considerably from one another. As regards the leaves, the earlier investigations of Schmiedeberg, Kiliani, Kraft, and others, indicated the presence of the following glucosides :—

Digitoxin (Schmiedeberg, Kiliani). Crystalline.
Digitalin (Schmiedeberg, Kiliani). Amorphous.
Digitalein (Kiliani). Amorphous.
Gitalin (Kraft). Amorphous.
Digitonin (Schmiedeberg). Amorphous.[1]
Digitonin (Kiliani). Crystalline.[2] } Saponins.

Recent investigations of Cloetta [3] show that digitalis leaves contain three definite, active, crystalline glucosides :—

Digitoxin, $C_{44}H_{70}O_{14}$.
Gitalin, $C_{17}H_{28}O_6$.
Bigitalin, $C_{40}H_{64}O_{14}$.

The gitalin of Kraft, and various substances formerly described as " digitalein," appear to be mixtures of gitalin and bigitalin. Gitalin and bigitalin are said to have about one-third of the physiological activity of digitoxin.

Digitalis seeds contain considerable proportions of saponins. One of the best-known preparations of the seeds is the so-called " digitalinum germanicum," obtained by extraction with alcohol and precipitation with tannin. Different investigators claim to have isolated from it the following products :—

Amorphous digitonin (Schmiedeberg).[4]
Crystalline digitonin (Kiliani).
Digitalin (Kiliani).
Digitoxin.
Digitalein.

[1] A mixture of saponins (Kraft, *Arch. Pharm.*, 1912, **250**, 118.
[2] Probably a mixture (Windaus and Schneckenburger, *Ber.*, 1913, **46**, 2628).
[3] *Arch. exptl. Path. Pharmacol.*, 1926, **112**, 261.
[4] A mixture of saponins (Kraft, *loc. cit.*).

Digitoxin, $C_{44}H_{70}O_{14}$, the " Digitaline cristallisée " of the Pharmacopée Française, is the main pharmacological constituent of digitalis leaves, in which it occurs to the extent of 0·2 to 0·4 per cent. It is a bitter, white, crystalline powder. On hydrolysis with boiling dilute hydrochloric acid, it is converted into digitoxigenin, a sugar (digitoxose, $C_6H_{12}O_4$), and another (and as yet unidentified) sugar.

Digitoxin is not appreciably soluble in water. In an infusion of digitalis leaves, it is believed to be present in the form of a colloidal suspension, brought about by the saponins present. Commercial digitoxin has to some extent replaced the crude drug and its galenicals as a cardiac tonic, but suffers from the disadvantage of being much more cumulative than the other digitalis glucosides.

The " digitalins " of commerce are variable mixtures obtained from the leaves or seeds by various processes. Some of them consist largely of digitoxin, but the digitalin of the British Pharmaceutical Codex (Digitalinum Pulverisatum Purum Germanicum) is said to be a mixture of all the glucosides of digitalis leaves, with the exception of digitoxin. It is not cumulative, and has the added advantage of being readily soluble in water.

Standardisation of digitalis preparations.—Preparations of digitalis are commonly standardised by injecting measured volumes into the ventral lymph sac of frogs, and so determining the minimum lethal dose (the minimum dose, per gram of body weight, required to kill a frog in a given time, usually 12 or 24 hours). A modification of this method, which has been adopted in the United States Pharmacopœia, is the determination of the minimum systolic dose (the minimum dose, per gram of body weight, required to produce, in one hour, a stoppage of the ventricle of the heart in systole).

Hatcher's intravenous cat method is a lethal dose method, the solution being injected into the femoral vein of the cat. It probably gives better results than the frog methods, but is, perhaps, not so convenient as a routine process.

Similar biochemical methods are employed for the standardisation of other drugs with digitalis-like actions, such as strophanthus and squill.

Squill glucosides.

The medicinal action of squill is due to the presence of glucosides, the earlier published accounts of which were very conflicting. The main glucosides were formerly believed to be two amorphous, toxic substances, scillitin and scilli-diuretin. More recently, a crystalline glucoside, **scillaren,** has been isolated,[1] and to it the typical cardiac-tonic and diuretic properties of the drug have been attributed. Scillaren is now being prepared from squill on the commercial scale.

According to Stoll[2] the total glucosides of squill consist of two-thirds of crystalline scillaren A and one-third of amorphous scillaren B. The crystalline glucoside, which is said to have the formula $C_{36}H_{52}O_{13}$, yields on hydrolysis scillaridin A, glucose, and rhamnose.

Gentian glucosides.

In 1905, Tanret isolated from fresh gentian root two crystalline glucosides, *gentiopicrin* and *gentiin*, and an amorphous glucoside, *gentiamarin*. During the drying of the root, under ordinary conditions, processes of fermentation take place, which result, apparently, in the gradual decomposition of the gentiopicrin.[3]

Gentiopicrin and gentiin are hydrolysed by mineral acids (gentiopicrin also by emulsin), and the reactions of hydrolysis have been represented by the following equations :—

$$\underset{\text{Gentiopicrin}}{C_{16}H_{20}O_9} + H_2O = \underset{\text{Gentiogenin}}{C_{10}H_{10}O_4} + \underset{\text{Glucose}}{C_6H_{12}O_6}$$

$$\underset{\text{Gentiin}}{C_{25}H_{28}O_{14}} + 2H_2O = \underset{\text{Gentienin}}{C_{14}H_{10}O_5} + \underset{\text{Glucose}}{C_6H_{12}O_6} + \underset{\text{Xylose}}{C_5H_{10}O_5}$$

Gentiamarin yields glucose and an amorphous substance on hydrolysis.

[1] *Chem. Farb. vorm. Sandoz*, E.P. 199400 and 217247.
[2] *Schweiz. Med. Woch.*, 1927, No. 49.
[3] Compare also Binaghi and Falqui, *Annali. Chim. Appl.*, 1925, **15,** 386.

DRUGS CONTAINING GLUCOSIDES.

Drug.	Botanical Source.	Glucosides and their Products of Hydrolysis.
Alderbuckthorn bark	*Rhamnus Frangula*	Frangulin → frangula emodin + rhamnose (see p. 60).
Bearberry leaves	*Arctostaphylos Uva-ursi*	Arbutin → quinol + glucose.
Bitter almonds	*Prunus Amygdalus* var. *amara*	Amygdalin → benzaldehyde + hydrocyanic acid + glucose (2 mols.).
Black haw bark	*Viburnum prunifolium*	Viburnin.
Black hellebore rhizome	*Helleborus niger*	Helleborein (a saponin) → acid and neutral helleboretins + acetic acid + glucose. Helleborin.
Black mustard seeds	*Brassica sinapioides*	Sinigrin → allyl iso-thiocyanate + potassium hydrogen sulphate + glucose.
Buchu leaves	*Barosma betulina*	Hesperidin → hesperetin + rhamnose + glucose.
Cherry-laurel leaves	*Prunus Laurocerasus*	Prulaurasin → benzaldehyde + hydrocyanic acid + glucose.
Digitalis leaves	*Digitalis purpurea*	Digitoxin → digitoxigenin + digitoxose + another sugar. Gitalin. Bigitalin. Digitonin (a mixture of saponins).
Gentian root	*Gentiana lutea*	Gentiopicrin → gentiogenin + glucose (in the fresh root). Gentiin → gentienin + glucose + xylose. Gentiamarin.
Horseradish root	*Cochlearia Armoracia*	Sinigrin → allyl iso-thiocyanate + potassium hydrogen sulphate + glucose.
Lily of the valley flowers	*Convallaria majalis*	Convallamarin → convallamaretin + glucose. Convallarins (acid and neutral saponins).
Linseed	*Linum usitatissimum*	Linamarin (a cyanogenetic glucoside).
Nux vomica seeds	*Strychnos Nux-vomica*	Loganin.
Picrorhiza rhizome	*Picrorhiza Kurroa*	Picrorhizin.
Quillaja bark	*Quillaja Saponaria*	Quillajic acid → quillajic sapogenin + glucose. Quillaja sapotoxin → quillaja sapotoxin sapogenin + glucose.
Red poppy petals	*Papaver Rhœas*	Mecocyanin (isomeric with cyanin, p. 63).
Red rose petals	*Rosa gallica*	Cyanin → cyanidin + glucose (see p. 63).

DRUGS CONTAINING GLUCOSIDES—*cont.*

Drug.	Botanical Source.	Glucosides and their Products of Hydrolysis.
Saffron	*Crocus sativus*	Crocin → crocetin + a sugar. Picrocrocin (see p. 64).
Sarsaparilla (Jamaica)	*Smilax ornata*	Sarsasaponin → sarsasapogenin + glucose.
Senega root	*Polygala Senega*	Polygalic acid. Senegin → senegenin + a sugar.
Squill	*Urginea Scilla*	Scillaren.
Strophanthus seeds	*Strophanthus Kombé*	*k*-Strophanthin → strophanthidin + a sugar
Urginea	*Urginea indica*	Probably similar to squill.
White mustard seeds	*Brassica alba*	Sinalbin → acrinyl iso-thiocyanate + sinapin hydrogen sulphate + glucose.
Wild cherry bark	*Prunus serotina*	Prunasin → benzaldehyde + hydrocyanic acid + glucose.
Willow bark	*Salix alba*	Salicin → saligenin + glucose.
Wintergreen leaves	*Gaultheria procumbens*	Gaultherin → methyl salicylate + glucose.

CHAPTER VI.

GUMS AND MUCILAGES.

Gums are, as a rule, produced by plants as a protective coating after injury. They are usually brittle, amorphous, transparent or translucent substances, which, on treatment with water, swell up, forming sticky gelatinous solutions or colloidal suspensions. Mucilages, such as occur in buchu leaves, bael fruit, slippery elm bark, marshmallow root, and the seeds of fenugreek, linseed, quince, and ispaghula are gum-like substances, and are sometimes distinguished from true gums by the fact that they occur as normal constituents of the plant instead of being formed as pathological products. The word mucilage is also used to denote aqueous solutions or suspensions of such substances as gums and starches.

Gums consist largely of "glucosidal acids," i.e. glucosidal substances of high molecular weight which possess acid properties, such as the power of forming metallic salts. On hydrolysis, these glucosidal acids yield less complex acids together with sugars.

Similar in chemical composition to gums are the pectins present in fruits, which cause the jellying of fruit juices. Commercial pectin is extracted from apple waste, and is used in the manufacture of jams and jellies.

Acacia gum (from species of *Acacia*) consists of a complex glucosidal acid, *arabin*, in combination with potassium, magnesium, and calcium. The free glucosidal acid can be prepared in the form of a colloidal suspension by acidifying a mucilage of gum acacia with hydrochloric acid and removing the metallic chlorides by dialysis. Arabin is a gummy substance which, after drying, swells up on addition of water without dissolving, but on treatment with dilute alkalis, it forms a solution or colloidal suspension of its alkali salts similar to mucilage of acacia.

On hydrolysis, arabin yields *arabic* or *iso-geddic acid*, together with arabinose and galactose.

Acacia gum contains an oxidase enzyme which is liable to cause undesirable reactions in dispensing, such as the formation of a blue colour with guaiacum resin.

Indian or **ghatti gum** (from *Anogeissus latifolia*) probably contains arabin and its metallic salts as its main constituents.

Distinction between Indian gum and acacia.—Prepare mucilages of Indian gum and acacia, using about 1 gram of gum and 10 c.cs. of water in each case. Add to each a solution of lead subacetate. The acacia gives a copious white precipitate, the Indian gum only a comparatively slight one. Note that no precipitate is produced when a solution of normal lead acetate is added to mucilages of either acacia or Indian gum.

Tragacanth (from species of *Astragalus*) differs from acacia and Indian gums in that it is not a pathological product, being pre-formed in the plant from the cell walls of the pith and medullary rays. It is a translucent, brittle substance, which swells in water, although only about 10 per cent. dissolves. The soluble portion consists mainly of a glucosidal acid, similar to arabin, which yields, on hydrolysis, geddic acid, arabinose, and galactose.

The insoluble portion of the gum is known as *bassorin*, and consists of glucosidal acids which yield, on hydrolysis, the sugars tragacanthose and xylose, together with bassoric acid.

Detection of acacia in powdered tragacanth.—To a mucilage of tragacanth add an aqueous solution of guaiacol, followed by a few drops of hydrogen peroxide. The mixture should remain colourless, but becomes reddish-brown on standing if acacia is present.

Detection of Indian gum in powdered tragacanth.—Make a mucilage by boiling 1 gram of tragacanth with 20 c.cs. of water. Add 5 c.cs. of concentrated hydrochloric acid, and boil for 5 minutes. The liquid should remain colourless, but develops a brown colour if Indian gum is present.

CHAPTER VII.

TANNINS AND RELATED SUBSTANCES.

TANNINS are exceedingly complex plant products, and before dealing with them it is necessary to mention briefly certain simple polyhydric phenols and acids which are produced as a result of their hydrolysis or decomposition.

Polyhydric phenols and polyhydroxy acids.

The simple polyhydric phenols are crystalline compounds, readily soluble in water, and are remarkable for the fact that, unlike the monohydric phenols, they are powerful reducing agents, and frequently yield complex, dark-coloured products on oxidation. Carboxylic acids derived from them also have powerful reducing properties; such acids generally lose carbon dioxide on gently heating, with formation of the parent phenols. These properties are well illustrated by the following typical substances.

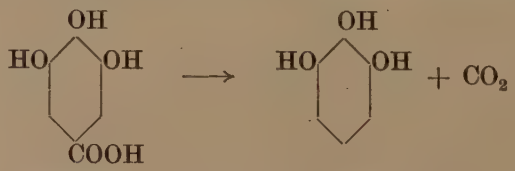
Gallic acid, or 3 : 4 : 5-trihydroxy-benzoic acid,

$$C_6H_2(OH)_3 \cdot COOH,$$

is the main product of the hydrolysis of oak gall tannin, and is usually prepared directly from oak galls by extraction with boiling dilute sulphuric acid.

Gallic acid is moderately soluble in water, from which it separates in small colourless needles containing $1H_2O$. It is a powerful reducing agent, and its aqueous solution yields, with ferric chloride, a blue-black coloration.

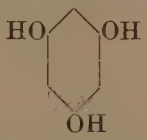
When gently heated, gallic acid loses carbon dioxide, with formation of the trihydric phenol pyrogallol (sometimes known as pyrogallic acid) :—



Gallic acid — Pyrogallol

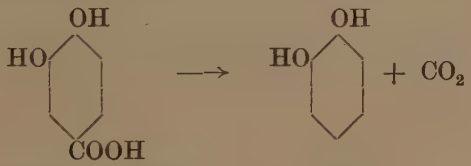
Pyrogallol, $C_6H_3(OH)_3$, is crystalline and freely soluble in water, and, like gallic acid, is a powerful reducing agent. Its alkaline solutions rapidly absorb oxygen with formation of complex dark-coloured oxidation products, a fact which is sometimes made use of in the estimation of oxygen in air and other gaseous mixtures. Aqueous solutions of pyrogallol give a blue-black colour with ferric chloride.

Isomeric with pyrogallol is *phloroglucinol*,



a crystalline compound which owes its name to the fact that it has a sweet taste.

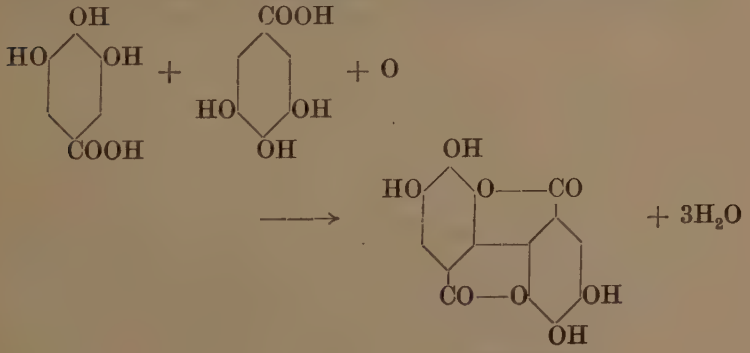
Protocatechuic acid, or 3 : 4-dihydroxy-benzoic acid, $C_6H_3(OH)_2 . COOH$, closely resembles gallic acid. On heating, it loses carbon dioxide with formation of *catechol:*



Protocatechuic acid — Catechol

Both protocatechuic acid and catechol are powerful reducing agents; they give green colorations with ferric chloride.

Ellagic acid, $C_{14}H_6O_8$, is formed by the hydrolysis of many tannins, and is closely related to gallic acid, from which it can be produced by the action of certain oxidising agents :—



Ellagic acid

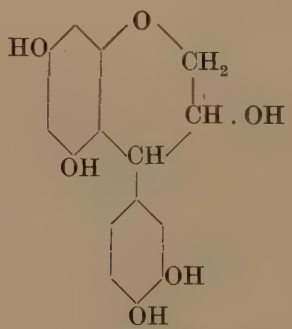
It may be noted that the " ellag " portion of the name was coined as the reverse of " galle."

Catechins.

Catechins are derivatives of polyhydric phenols which occur in cutch, gambier, red gum, and other drugs. They are well-defined crystalline compounds of definite melting-point. The catechins present in different drugs are not identical, although they are all similar in chemical properties.

Catechins are soluble in water, and give characteristic colorations with ferric salts. Their alkaline solutions rapidly absorb atmospheric oxygen with formation of dark-coloured products. They are decomposed when heated with dilute acids under pressure, with formation of catechol and phloroglucinol, and boiling water slowly converts them into a series of anhydrides of which little is known.

The catechins have been investigated by Freudenberg, Nierenstein, and others, but the results are somewhat conflicting. *Acacatechin*, present in cutch (*Acacia Catechu*), has been synthesised by Nierenstein,[1] who has assigned to it the following structure :—



Acacatechin

The other catechins are doubtless similar in constitution.

Tannins.

Tannins have certain important characteristics in common. They are capable of converting hides into leather,

[1] *Trans. Chem. Soc.*, 1921, **119**, 164.

they have astringent tastes, and they give green or blue-black colorations with ferric salts. Tannins are of very wide occurrence in drugs, and are of medicinal importance on account of their astringent action.

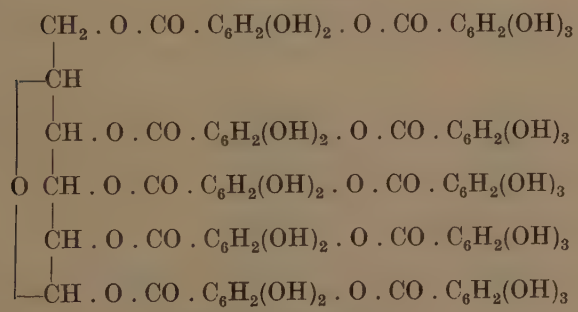
Tannins are usually amorphous, and are exceedingly difficult to purify. Consequently, in spite of the extensive researches of Emil Fischer, Freudenberg, Nierenstein, and others,[1] the constitutions of most of them are still unknown or in a state of considerable doubt. Some tannins are glucosidal substances, but others are not.

Gallotannin, the "tannic acid" of the British and United States Pharmacopœias, is usually extracted from powdered galls by means of ether containing alcohol and water. The liquid separates on standing into two layers, of which the lower contains gallotannin, the free gallic acid which is always present in galls remaining in the upper layer. After separation, the solution of gallotannin is evaporated, and the product may be further purified in various ways.

Gallotannin is met with in the form of straw-yellow glistening scales, freely soluble in water. It has the approximate empirical formula $C_{14}H_{10}O_9$, but the investigations of Fischer [2] seem to show that pure gallotannin (from Chinese galls) is penta-digalloyl glucose, a condensation product of one molecule of glucose with five of digallic acid :—

$$C_6H_2(OH)_3 . CO . O . C_6H_2(OH)_2 . COOH$$

Digallic Acid



Penta-digalloyl glucose

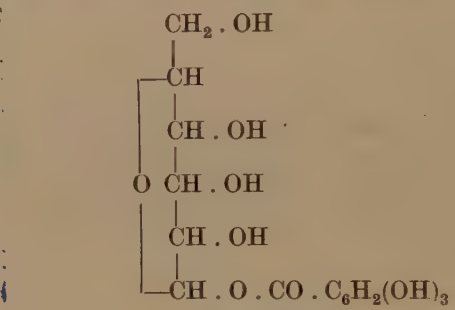
[1] Numerous papers since about 1905, mostly in the *Berichte.*

[2] *Ber.*, 1912, **45,** 915, 2709; 1913, **46,** 1116; 1914, **47,** 2485; 1918, **51,** 1760; 1919, **52,** 829.

Owing to the absence of any criterion of the purity of an amorphous substance like gallotannin, the above formula, though commonly accepted, is not above suspicion, and some investigators maintain that pure gallotannin yields no glucose on hydrolysis, and is, therefore, not a glucose derivative.[1]

The gallotannin obtained from Turkish galls is similar to, but probably not identical with, that from Chinese galls.

Glucogallin occurs in Chinese rhubarb, and is a crystalline compound of definite melting-point. It is a comparatively simple compound, being β-galloyl glucoside :—



Glucogallin

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Glucogallin has been prepared synthetically,[2] and is said to be the only natural tannin of which the chemical structure is definitely known.

A few other natural tannins have been obtained crystalline, and of these may be mentioned hamamelitannin (from *Hamamelis virginiana*) and chebulinic acid (from *Terminalia Chebula*).

Classification of tannins.—Many systems of classification have been proposed, based either on empirical tests, products of decomposition, or considerations of supposed chemical structure. No one of these systems has received general approbation, but the tannins may be said to fall roughly into the following groups :—

Pyrogallol tannins.—These give blue-black colorations with ferric salts, and yield, on heating, a sublimate of pyrogallol. When boiled with dilute hydrochloric acid they are

[1] Mitchell, *Analyst*, 1923, **48**, 2. Nierenstein, *Analyst*, 1923, **48**, 321 ; *Ber.*, 1923, **56**, 1876.

[2] Fischer and Bergmann, *Ber.*, 1918, **51**, 1760.

hydrolysed with formation of either gallic or ellagic acid, and this makes it possible to subdivide the class into gallitannins and ellagitannins.

Phlobatannins.—These give green colorations with ferric salts, and yield catechol on heating. When boiled with dilute hydrochloric acid they are converted into red insoluble substances known as phlobaphenes, and their behaviour in this way differs remarkably from that of the pyrogallol tannins.

The **phlobaphenes** are amorphous, and sparingly soluble in water. They appear to be anhydrides of the phlobatannins. Most drugs containing phlobatannins also contain varying proportions of phlobaphenes, and liquid preparations of such drugs sometimes deposit gelatinous magmas containing phlobaphenes. Naturally occurring phlobaphenes are believed to be considerably different from those produced from phlobatannins by the action of acids.

Detection of tannins.—A large number of tests have been used for the detection of tannins in drugs and their preparations. Of these, the most important are the precipitation of tannins by gelatin and by alkaloids, the formation of colorations or coloured precipitates with iron salts, and the tanning of Goldbeaters' skin. Of these tests, only the last can be said to be definitely specific.

The ferric salt reaction.—Prepare a dilute solution of ferric acetate by mixing aqueous solutions of ferric chloride and sodium acetate. Add two or three drops of this reagent to a solution of gallotannin, when a blue-black precipitate will be produced.

Goldbeaters' skin test.—Soak about a square inch of Goldbeaters' skin in 2 per cent. hydrochloric acid for a few minutes. Rinse with distilled water and immerse in a solution of gallotannin for 5 minutes. Rinse again, and immerse in a 1 per cent. solution of ferrous sulphate, when the tanned skin will become dark brown or black. By more elaborate modifications of this simple test, it is possible to detect the presence of small quantities of tannins in drugs.

By the application of the Goldbeaters' skin test, the following drugs have been shown to give unmistakable indications of the presence of tannins :—[1]

Acacia bark.	Cinchona bark.
Bearberry leaves.	Cloves.
Butea gum.	Cocoa seeds.
Cinnamon bark.	Cutch.

[1] Jordan and Ware, *Y.B. Pharm.*, 1924, 651.

Galls.
Gambier.
Guarana.
Kino (Malabar).
Krameria root.
Myrobalans.
Oak bark.
Red gum (Eucalyptus Kino).
Red rose petals.
Rhubarb rhizome.
Tea leaves.
Virginian prune bark.
Willow bark.
Witch-hazel bark.
Witch-hazel leaves.

The following table includes the more important drugs which are employed partly or wholly on account of the astringent action of the tannins they contain. The proportions given of the various constituents must in some cases be accepted with reserve :—

Drugs Containing Tannins.

Class.	Drug.	Botanical Source.	Constituents.
Drugs containing pyrogallol tannins	Galls	*Quercus infectoria*	Gallotannin (50-60 %), gallic acid (2-4 %), ellagic acid, sugars.
	Witch-hazel bark and leaves	*Hamamelis virginiana*	Hamamelitannin (6 %), gallic acid.
	Myrobalans	*Terminalia Chebula*	Tannin, 27-33 % (chebulinic acid), gallic acid.
Drugs containing phlobatannins	Acacia bark	*Acacia arabica* and *A. decurrens*	Tannin (22 %), gallic acid. *A. arabica* contains a gallitannin as well as a phlobatannin.
	Butea gum	*Butea frondosa*	Kinotannin (15-62 %).
	Cutch	*Acacia Catechu*	Catechutannin (14-54 %), catechins (2-40 %), gum (20-30 %).
	Gambier	*Uncaria Gambier*	Catechutannin (20-50 %), catechins (7-33 %), gum (10-16 %).
	Kino (Malabar)	*Pterocarpus Marsupium*	Kinotannin (70-80 %), kino-red (phlobaphene), catechol, gallic acid
	Oak bark	*Quercus robur*	Quercitannin (5-20 %), oak red (phlobaphene), gallic acid, ellagic acid.
	Red gum	*Eucalyptus rostrata* and other species	Kinotannin (40-50 %), kino-red (phlobaphene), catechins, catechol.
	Rhatany root	*Krameria triandra* and *K. argentea*	Krameriatannin (8-21 %), krameria red (phlobaphene). The root from *K. triandra* contains more alcohol-soluble substances than that from *K. argentea*.

CHAPTER VIII.

PHLOROGLUCINOL DERIVATIVES.

MALE fern rhizome, kousso flowers, and embelia fruits are drugs which may be conveniently dealt with together. Their anthelmintic action is due to the presence of complex substances which can be decomposed with formation of derivatives of the trihydric phenol phloroglucinol (p. 47).

Male fern rhizome (*Dryopteris Filix-mas*) contains a number of derivatives of phloroglucinol, some of which are undoubtedly very complex in constitution. Good extracts of the rhizome have been found to contain :—[1]

Filicic acid . .	3·5 per cent.
Flavaspidic acid .	2·5 ,,
Albaspidin . .	0·05 ,,
Aspidinol . .	0·1 ,,
Flavaspidin . .	0·1 ,,
An amorphous acid .	5·0 ,,
Filicinigrins . .	6·0 ,,

The anthelmintic action of the drug is attributed to the amorphous acid, which has been termed filmarone.[2]

Filmarone, $C_{47}H_{54}O_{16}$, is a complex dibasic acid. When heated with zinc dust and aqueous sodium hydroxide, it yields various derivatives of phloroglucinol, together with butyric acid. In this connection it is interesting to note that all known tænicides, with the exception of the alkaloids of pomegranate root, are butyric or isobutyric acid derivatives.[3]

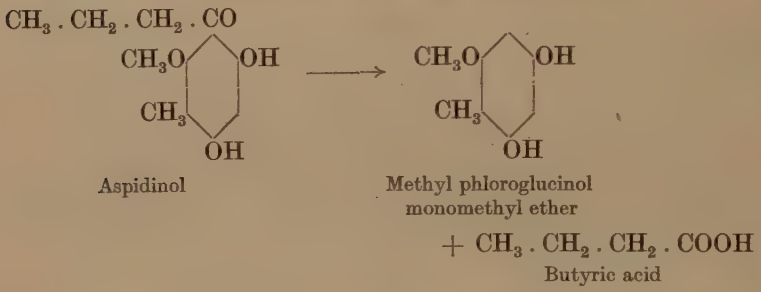
Filmarone slowly decomposes in male fern rhizome and

[1] Kraft, *Chem. Centralblatt*, 1902, ii. 533.
[2] Kraft, *Arch. Pharm.*, 1904, **242**, 489.
[3] Karrer, *Helv. Chim. Acta*, 1919, **2**, 466.

its preparations, with formation of filicic acid and other physiologically inactive products. On this account, extracts of male fern deposit crystalline filicic acid on keeping, at the same time becoming less active.

Filicic acid is a yellow crystalline compound of complex constitution, which appears to have no marked anthelmintic properties.

Aspidinol is a comparatively simple compound which yields, when digested with zinc dust and caustic soda, methyl phloroglucinol monomethyl ether and butyric acid :—



Aspidinol

Methyl phloroglucinol monomethyl ether

Butyric acid

The *filicinigrins* are decomposition products of the other constituents of male fern rhizome. They form a brown or black amorphous powder, which is physiologically inactive.

Assay of male fern and its preparations.—Various pharmacopœias prescribe methods for the estimation of "filicin" in male fern rhizome and its liquid extract. From the nature of the processes, it is evident that the extracted "filicin" is a mixture of acidic constituents.

Dissolve 5 grams of well-stirred liquid extract of male fern in 40 c.cs. of ether, and transfer to a 200 c.c. separating funnel. Add 100 grams of a 3 per cent. solution of barium hydroxide, and shake vigorously for several minutes. Allow the liquids to separate, and filter off 86 grams of the aqueous layer. Transfer this to a separating funnel, acidify with hydrochloric acid, and extract with three successive quantities of ether (30, 20, and 15 c.cs.). Filter the mixed ethereal extracts, wash the filter paper with a little ether, evaporate in a tared dish, dry at 100°, and weigh.

Of the 86 grams of aqueous extract taken, about 6 grams consist of dissolved ether; hence, the weight of the residue may be assumed to correspond to four-fifths of the total weight of "filicin" in the 5 grams of liquid extract originally taken.

Kousso flowers (*Brayera anthelmintica*) contain, as the principal anthelmintic constituent, an amorphous substance known as *kosotoxin*. The drug also contains α- and β-kosins,

protokosin, and kosidin, all of which are crystalline substances which appear to be physiologically inactive.

The close relationship of kosotoxin to the constituents of male fern is shown by the fact that it yields, on heating with zinc dust and sodium hydroxide, trimethylphloroglucinol and butyric acid.

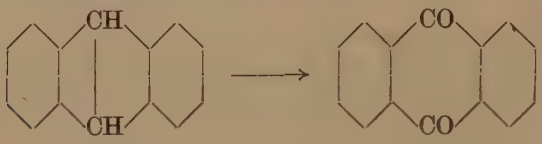
Embelia fruit (*Embelia Ribes* and *E. robusta*) contains a crystalline compound, *embelic acid*, to which the action of the drug is due. Embelic acid is closely related to the constituents of male fern and kousso.

Detection of embelic acid.—Shake some powdered embelia fruit with ether in a test tube. Decant off the clear liquid and add to it a few drops of dilute ammonia, when a bluish-violet precipitate is produced in the ammoniacal layer.

CHAPTER IX.

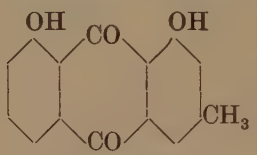
ANTHRAQUINONE DERIVATIVES.

ANTHRAQUINONE is the diketone produced by oxidation of the hydrocarbon anthracene :—



Anthracene Anthraquinone

Many purgative drugs, such as rhubarb, senna, cascara, and aloes, contain derivatives of anthraquinone, which are present either in the free state or as glucosides. One of the simplest of these compounds is the so-called " chrysophanic acid," which is 1 : 8-dihydroxy-3-methyl anthraquinone :—

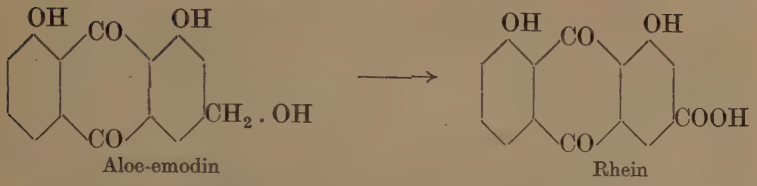


Chrysophanic acid

This formula has been confirmed by synthesis.[1] It will be noticed that chrysophanic acid is a phenolic compound, and not a carboxylic acid, and is, therefore, better known as chrysophanol.

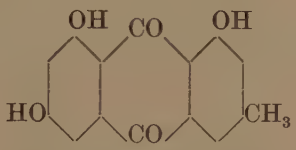
Derived from chrysophanic acid are aloe-emodin (which contains a primary alcohol group) and rhein (the corresponding carboxylic acid). Rhein can be prepared from aloe-emodin by oxidation :—

[1] Eder and Widmer, *Helv. Chim. Acta*, 1922, **5**, 3 ; 1923, **6**, 419.



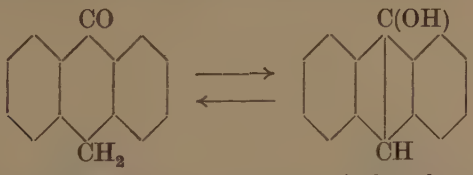
Aloe-emodin Rhein

Emodin (frangula-emodin) is a hydroxy-chrysophanic acid, the structure of which as 1 : 6 : 8-trihydroxy-3-methyl anthraquinone has been confirmed by two independent syntheses :—[1]



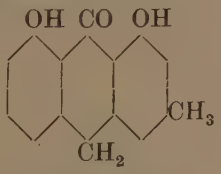
Emodin (frangula-emodin)

Partially reduced derivatives of anthraquinone (the anthrones and anthranols) also occur in drugs. Compounds of these two types are isomeric, and in many cases intra-convertible, the change from one to another merely involving the movement of a hydrogen atom :—[2]



Anthrone Anthranol

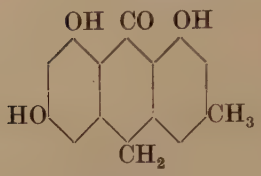
Typical naturally occurring anthrones are chrysophanolanthrone, and emodinanthrone and its monomethyl ether :—



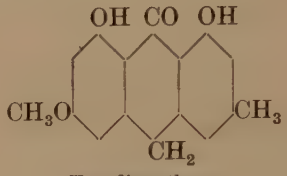
Chrysophanolanthrone

[1] Eder and Widmer, *Helv. Chim. Acta*, 1923, **6**, 966 ; Jacobson and Adams, *J. Amer. Chem. Soc.*, 1924, **46**, 1312. Compare Eder and Hauser, *Helv. Chim. Acta*, 1925, **8**, 126.

[2] Compare K. H. Meyer, *Annalen*, 1911, **379**, 37.

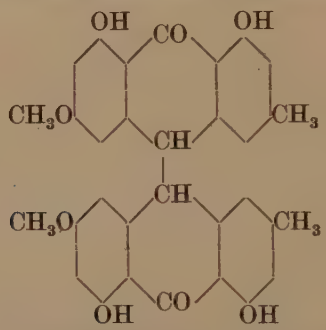


Emodinanthrone



Emodinanthrone monomethyl ether

Some of the more complex naturally occurring anthracene derivatives contain two anthracene nuclei joined together. Of such a type is dehydro-emodinanthrone monomethyl ether (1 : 8 : 1′ : 8′-tetrahydroxy-3 : 3′-dimethyl-6 : 6′-dimethoxy-dianthrone), which is present in araroba :—



Dehydro-emodinanthrone monomethyl ether

In the case of such drugs as rhubarb, senna, and cascara, the proportions of the anthraquinone derivatives known to be present are often insufficient to account for the purgative action of the drug, which in such cases is not completely understood.

Test for drugs containing hydroxy-methyl-anthraquinones.—Boil about 0·1 gram of the drug (powdered rhubarb, for example) with 10 c.cs. of dilute sulphuric acid, cool, filter, and shake the filtrate gently with ether. Separate the ethereal layer, and add to it dilute ammonia. A red colour develops in the ammoniacal layer, and is said to be due to the presence of emodin. In carrying out the test, amyl alcohol, carbon tetrachloride, or benzene may be used instead of ether.

Colour reactions capable of distinguishing between senna, rhubarb, aloes, cascara, and frangula are described in the literature.[1]

[1] Beal and Okey, *J. Amer. Chem. Soc.*, 1917, **39**, 716 ; Hubbard, *J. Ind. Eng. Chem.*, 1917, **9**, 518.

Rhubarb rhizome (*Rheum officinale* and *R. palmatum*) contains numerous anthraquinone derivatives, both in the free state and as glucosides, the most important being emodin and chrysophanic acid, with smaller proportions of emodin monomethyl ether, aloe-emodin and rhein. The chief purgative constituent appears, however, to be a complex non-glucosidal resin, present to the extent of about 10 per cent., which yields anthraquinone derivatives on hydrolysis.[1]

The astringent constituents of rhubarb are glucosidal tannins which, on hydrolysis, yield gallic acid, glucose, and other products.

Rhubarb also contains oxalic acid, mainly as its calcium salt. About 7 per cent. of calcium oxalate is frequently present, and can be seen easily under the microscope in the form of rosette crystals.

English rhapontic rhubarb (*Rheum rhaponticum*) contains chrysophanic acid and other anthraquinone derivatives, but, apparently, no emodin, aloe-emodin, or rhein. It can be distinguished from Chinese rhubarb by the fact that it contains a crystalline glucoside *rhaponticin*.[2]

Detection of rhapontic rhubarb.—Shake about 0·5 gram of the powdered drug with 2 per cent. ammonia, and keep the mixture at 25°-30° for 15 minutes. Filter on to a watch-glass and set aside, when crystals of rhaponticin separate. This test serves to distinguish rhapontic rhubarb from the Chinese variety. More delicate tests, capable of indicating the presence of as little as 5 per cent. of rhapontic rhubarb in Chinese, are described in the literature.[3]

Senna leaves (*Cassia acutifolia* and *C. angustifolia*) contain a variable proportion (usually about 1 per cent.) of rhein and aloe-emodin, partly in the free state and partly as glucosides. The investigations of Tutin[4] indicate that these are the only anthraquinone derivatives present in any quantity.

The leaves also contain a yellow crystalline compound, *kaempferol*, $C_{15}H_{10}O_6$, partly free and partly as its glucoside, *kaempferin*. Kaempferol is a derivative of flavone (p. 62), which is the parent substance of many natural colouring matters. *Iso-rhamnetin*, $C_{16}H_{12}O_7$, another yellow flavone derivative, has been isolated from some varieties of senna leaves.

[1] Tutin and Clewer, *Trans. Chem. Soc.*, 1911, **99,** 946.
[2] Tschirch and Cristofoletti, *Arch. Pharm.*, 1905, **243,** 443.
[3] See Joachimovitz, *Y.B. Pharm.*, 1924, 291.
[4] *Trans. Chem. Soc.*, 1913, **103,** 2006.

Calcium oxalate and calcium tartrate are also present in senna leaves.

Senna fruit contains anthraquinone derivatives, and the active constituents are probably the same as, or similar to, those of the leaves.

Alder buckthorn or **frangula bark** (*Rhamnus Frangula*) contains as its main constituent emodin (frangula-emodin), mostly combined with rhamnose as a crystalline glucoside frangulin. Chrysophanic acid and an iso-emodin are also said to be present. It has recently been suggested that the active purgative principle is an amorphous glucoside, *glucofrangulin*, which splits up on hydrolysis into glucose, rhamnose, and emodin.[1]

Cascara bark (*Rhamnus Purshianus*) contains emodin, and, no doubt, other anthraquinone derivatives, both free and as glucosides, but the nature of the active constituents is not properly known.

The bitter taste of the bark is due to a substance, probably a lactone, which can be converted into less bitter metallic salts. Methods for the preparation of non-bitter extracts of cascara depend on this fact.

Araroba powder (*Andira Araroba*), as imported in the crude state, contains from 14 to 67 per cent. or more of anthraquinone, anthrone, and anthranol derivatives, together with vegetable débris and water. Chrysarobin, or purified araroba, is prepared by extracting crude araroba with boiling benzene, filtering from insoluble matter, and crystallising from the filtrate.

Chrysarobin has been the subject of several investigations, and has been found to consist chiefly of anthrones or anthranols, with much smaller proportions of substituted anthraquinones (emodin, etc.). The main constituents appear to be chrysophanolanthrone (29-39 per cent.), emodinanthrone monomethyl ether (18-20 per cent.), and dehydro-emodinanthrone monomethyl ether (22-35 per cent.).[2]

Detection of chrysarobin.—Spread a few milligrams of the powder on a white tile. Add one or two drops of fuming nitric acid. Drop a little dilute ammonia on the tile, so that the liquids gradually mix. An evanescent, intense

[1] Casparis and Maeder, *Schweiz. Apoth. Ztg.*, 1925, **63**, 313.

[2] Eder and Hauser, *Arch. Pharm.*, 1925, **203**, 321. Compare Tutin and Clewer, *Trans. Chem. Soc.*, 1912, **101**, 290; and Hesse, *Annalen*, 1917, **413**, 350.

violet colour is produced at the junction of the liquids. This test serves to distinguish chrysarobin (or araroba) from other drugs containing anthraquinone derivatives.

Aloes (from various species of *Aloe*) contain, as their main active constituent, the aloins, of which the most important is *barbaloin*, a crystalline glucoside derived from aloe-emodin and *d*-arabinose.[1] Barbaloin occurs in all common commercial forms of aloes, but is absent from the now rarely met with Natal variety. Curaçao aloes contains, in addition, crystalline *iso-barbaloin*, the presence of which is characteristic of this variety. The percentage of crystalline aloins in different varieties of aloes varies from about 10 to 30 per cent. or more.

An amorphous aloin, known as *β-barbaloin*, is present in all varieties of aloes, particularly the Cape. It is formed when crystalline barbaloin is heated at 160°-165°.[2]

Aloes also contains considerable quantities of resin, composed of resinotannols (p. 121), combined with cinnamic or *p*-hydroxy-cinnamic (*p*-coumaric) acids.[3]

Tests for aloes.—1. *General test for aloes.*—Dissolve a little aloes in boiling water, and add powdered borax to the boiling liquid. Pour the dark solution, drop by drop, into a test tube of water, and note the green fluorescence. This fluorescence is due to the presence of barbaloin, and is therefore given by all varieties of aloes except the Natal.

2. *Cupraloin test for Curaçao aloes.*—Dissolve in boiling water, and dilute to give about a 1 in 1000 solution. To 10 c.cs. of this solution add a drop of 5 per cent. copper sulphate solution, sodium chloride, and a little alcohol, and warm gently. Note the reddish-violet colour, due to the presence of iso-barbaloin. The colour remains, even after standing for 24 hours. Under similar conditions Socotrine and Zanzibar aloes give no colour, and Cape aloes only a faint evanescent pink.

3. *Nitric acid tests.*—Treat powdered samples of the different varieties of aloes, on a white tile, with concentrated nitric acid. Note the colours: Curaçao, crimson; Socotrine and Zanzibar, reddish-brown; Cape, green (slowly developed).

Cassia pods (*Cassia Fistula*) contain anthraquinone derivatives, of which little is known.

[1] See Tschirch, *Handbuch der Pharmacognosie*, Band II., Abteilung 2, p. 1434.

[2] Léger, *Compt. rend.*, 1907, **145,** 1179.

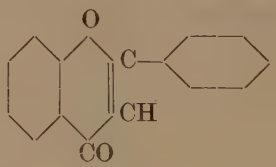
[3] Tschirch and Hoffbauer, *Arch. Pharm.*, 1905, **243,** 399.

CHAPTER X.

COLOURING MATTERS.

Coloured organic compounds are widely distributed in nature. The leaves of most plants contain the green colouring matter *chlorophyll*, which has an important photocatalytic effect on the processes of plant metabolism. The chemistry of chlorophyll has been very fully investigated by Willstätter and others,[1] and it has been shown that ordinary chlorophyll is a mixture of two complex magnesium compounds, chlorophyll *a* and chlorophyll *b*, to which have been assigned the respective formulæ $C_{55}H_{72}O_5N_4Mg$ and $C_{55}H_{70}O_6N_4Mg$.

The other natural colouring matters are of the most varied chemical nature. The colours of many flowers and fruits are due to the presence of derivatives of *flavone*:—



Flavone

Flavone itself has been found in several varieties of *Primula*, and of its more important derivatives may be mentioned scoparin (in broom tops), kaempferol and iso-rhamnetin (in senna leaves), and quercetin (in the bark of certain varieties of oak, in buckthorn berries, and in bearberry leaves, either in the free state or as the glucoside quercitrin). The *anthocyans*, which produce the violet, blue, and red colours of

[1] See *J. Amer. Chem. Soc.*, 1915, **37**, 323.

many flowers, are glucosides derived from anthocyanidins and various sugars. The anthocyanidins are compounds closely related to flavone.

Many plant products containing colouring matters are, or have been in the past, used in dyeing or in the manufacture of pigments, and among these may be mentioned indigo, madder, logwood, fustic, weld, gamboge, cutch, and gambier ; some colouring matters such as litmus, turmeric, and cochineal are used as indicators. It is only necessary to describe here such coloured constituents of drugs as are of pharmaceutical importance.

Red rose petals (*Rosa gallica*).—The colour of red rose petals is due to the presence of *cyanin*, a glucoside derived from glucose and the anthocyanidin *cyanidin*. An aqueous infusion of red rose petals is turned a deeper red by the addition of acids, but becomes greenish-yellow with alkalis.

When present in plants as a potassium salt, cyanin produces a blue colour (as in blue cornflowers).

Red poppy petals (*Papaver Rhœas*) contain *mecocyanin*, which is an anthocyan isomeric with cyanin.

Logwood (*Hœmatoxylon campechianum*).—Freshly cut logwood contains a colourless crystalline compound, *hæmatoxylin*, $C_{16}H_{14}O_6$. For dyeing purposes the ground wood is " aged," or fermented, by moistening and exposing to the atmosphere, when the hæmatoxylin becomes oxidised to a quinonoid compound, *hæmatein*, $C_{16}H_{12}O_6$, the wood at the same time acquiring a beetle-green lustre :—

$$2C_{16}H_{14}O_6 + O_2 = 2C_{16}H_{12}O_6 + 2H_2O.$$

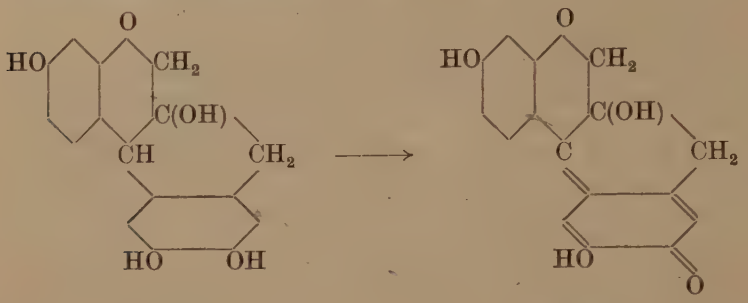
Hæmatoxylin is sparingly soluble in water, but dissolves in alkalis, forming purple solutions.

Hæmatein is the true colouring matter of " aged " logwood, and has feeble acid properties. Over-ageing of the wood results in the further oxidation of the hæmatein to brownish compounds which have no dyeing properties.

For medicinal use the unaged wood, containing about 10 per cent. of hæmatoxylin and comparatively little hæmatein, is used.

Sappan wood (*Cæsalpinia Sappan*) contains the colourless or pale yellow crystalline compound *brazilin*, $C_{16}H_{14}O_5$, which, by ageing of the wood, becomes converted into the deep red quinonoid compound *brazilein*, $C_{16}H_{12}O_5$.

Using the accepted structural formulæ,[1] the change may be represented as follows :—



Brazilin Brazilein

Hæmatoxylin and hæmatein (see logwood) are hydroxy derivatives of brazilin and brazilein respectively.

Red sanders wood (*Pterocarpus santalinus*) contains a red colouring matter, *santalin*, together with deoxysantalin. The colouring matter of red sanders wood, unlike those of logwood and sappan wood, is insoluble in water. It is, however, soluble in alcohol, the solution becoming violet on the addition of alkali.

Colour reactions.—*Logwood.*—Treat a decoction with lime water and note the blue-violet colour produced.

Sappan wood.—Treat a decoction with lime water and note the carmine colour.

Red sanders wood.—Extract the colouring matter with alcohol and treat the solution with alcoholic sodium hydroxide. Note the violet colour.

Alkanet root (*Alkanna tinctoria*) contains a colouring matter known as alkannin, which is probably a mixture. Alkannin is insoluble in water, but dissolves in alcohol and in fatty and volatile oils. The alcoholic solution is crimson, and changes to blue on addition of alkalis, the crimson colour being restored on acidification.

A freshly prepared dilute tincture of alkanet is used to stain fats and oils for their microscopical detection.

Saffron (*Crocus sativus*) contains the yellow glucoside *crocin*, $C_{44}H_{70}O_{28}$ (?), which on hydrolysis yields the red colouring matter crocetin, $C_{34}H_{46}O_9$. A second glucoside, picrocrocin, is said to be present. Saffron is frequently

[1] See Crabtree and Robinson, *Trans. Chem. Soc.*, 1918, **113**, 859.

adulterated, and for this purpose safflower and calendula florets and red poppy petals have been used.

Cochineal (*Coccus cacti*) contains from 10-20 per cent. of a red crystalline glucoside, *carminic acid*, $C_{22}H_{20}O_{13}$, which, on boiling with dilute acids, is hydrolysed with formation of carmine red, $C_{11}H_{12}O_7$. Carminic acid is soluble in both water and alcohol.

Tincture of cochineal is used as an indicator in volumetric analysis, notably in alkaloidal estimations. It gives a yellow colour in acid solution and a lilac in alkaline.

Commercial carmine is a red pigment prepared from cochineal in various ways. In one process a decoction is made by boiling the insects with aqueous potassium carbonate. Powdered alum is added, and, after allowing to settle, the clear liquid is decanted, treated with isinglass, and heated to precipitate the pigment.

The lac-dye obtained from the insect *Coccus lacca* contains a colouring matter, *laccaic acid*, which is similar to, but not identical with, carminic acid.

CHAPTER XI.

ALKALOIDS.

The term "alkaloid" has altered in significance with the course of time, and is, even now, incapable of precise definition. Originally meaning "alkali-like," it was applied indiscriminately to all organic bases, but at the present time it is usually restricted to cyclic nitrogenous bases which occur in plants.[1] Many basic substances occur in animals, but these are usually widely different in chemical structure from the plant alkaloids, and are, with few exceptions, of little medicinal importance.

In recent years many of the common alkaloids have been prepared synthetically in the laboratory. In addition, many compounds have been synthesised which, though closely related to the plant alkaloids in chemical structure, have not been isolated from any natural source ; such compounds are often known as "synthetic alkaloids," and some of them, such as benzamine or β-eucaine, are widely used in medicine.

Most alkaloids are colourless solids, which crystallise well. A few exceptions to this general statement may be recorded here : coniine, pelletierine and iso-pelletierine, nicotine (from *Nicotiana Tabacum*), and sparteine are liquids ; berberine is a yellow solid, and some of the alkaloids of bloodroot (sanguinarine and chelerythrine) form coloured salts, although the bases themselves are colourless. Many alkaloids are optically active, and these, as found naturally, are usually lævorotatory.

Chemically, alkaloids behave as secondary or tertiary amines, and many of them are strong bases and can be

[1] An interesting theory of the mechanism of the formation of alkaloids in plants is given by Robinson, *Trans. Chem. Soc.*, 1917, **111**, 876.

accurately estimated by titration with acids. Most of them are insoluble or sparingly soluble in water, but combine with acids to form salts which are freely soluble. From solutions of their salts, they are precipitated by addition of alkalis, although it should be noted that a compound like morphine, which is a phenol as well as a base, will dissolve in excess of caustic alkalis with formation of metallic derivatives. As a rule, alkaloids are soluble in such organic solvents as chloroform and ether, but their salts are not—a fact which is commonly made use of in the extraction of alkaloids from plants and in their estimation in drugs and galenicals.

Extraction and estimation of alkaloids.—The isolation of alkaloids from plants necessitates their separation from tannins, acids, resins, fats, colouring matters, and other non-basic substances which may be present. As a rule, the alkaloids are present in the form of salts, and the first step in the process of extraction consists in liberating the free bases from the ground drug by means of calcium hydroxide, or some other suitable alkali. The alkaloids are then extracted with an immiscible organic solvent, such as chloroform, ether, or light petroleum. This extract, which contains resins, fats, and other substances, is shaken with a dilute acid, when the alkaloids form soluble salts, which pass into solution in the aqueous layer. From the separated solution of alkaloidal salts, the free bases are liberated by addition of alkali, and are finally extracted by means of an immiscible organic solvent, which is recovered by distillation. In the case of most drugs, such a process yields a mixture of alkaloids, which may be separated by chemical methods or, more commonly, by fractional crystallisation of the free bases or their salts.

Alkaloids are usually estimated in drugs and galenicals by extracting them in some such way as that outlined above, and finally weighing or titrating the alkaloidal residue. The indicators most commonly used in alkaloidal estimations are cochineal, methyl red, and methyl orange, but bromophenol blue, bromocresol purple, hæmatoxylin, and other indicators are sometimes employed. The literature on alkaloidal estimations is voluminous, and cannot be gone into here. Methods for the assay of the more important drugs and galenicals are described in the pharmacopœias of different countries, and reference should be made to these.

Quantitative isolation of an alkaloid from its salt.—The following simple quantitative experiment will illustrate the principle of the general process of extraction or estimation of alkaloids.

Weigh about 0·25 gram of quinine sulphate, dissolve in water containing a little dilute sulphuric acid, and transfer to a separating funnel. Add ammonia until the liquid is slightly alkaline, in order to precipitate the free alkaloid. Extract the alkaloid with three successive quantities of chloroform (15, 10, and 10 c.cs.). Wash the mixed chloroform extracts with water in a clean separating funnel, and transfer to a small tared beaker. Evaporate off the chloroform on a water bath, dry the beaker and contents in a water oven, and weigh. The weight of residue should represent 73·5 per cent. of the weight of quinine sulphate originally taken.

Dilute solutions of alkaloidal salts form precipitates with various reagents, such as potassium mercuric iodide, potassium bismuth iodide, picric acid, gallotannin, gold and platinum chlorides, potassium ferro- and ferri-cyanides, and iodine in potassium iodide solution. Some of these precipitates have characteristic crystalline forms and definite melting-points, and their preparation provides a valuable method for the detection and identification of alkaloids. For instance, a method has been devised for the identification of a large number of alkaloids by the microscopical appearance of their picrates.[1]

Precipitation tests for alkaloids.—These tests may be applied to solutions of any of the common alkaloids in the minimum quantity of dilute hydrochloric acid.

Mayer's reagent (made by adding potassium iodide to mercuric chloride solution until the precipitate first formed just re-dissolves) gives yellowish-white precipitates with all common alkaloids except those of the purine group.

Dragendorff's reagent (made by dissolving bismuth oxy-nitrate in hydrochloric acid and adding potassium iodide until the precipitate first formed re-dissolves [2]) gives orange or brownish-red precipitates with most common alkaloids.

Wagner's reagent (iodine dissolved in aqueous potassium iodide) gives red or reddish-brown precipitates with nearly all alkaloids except those of the purine group.

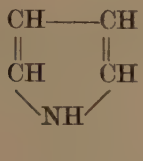
Hager's reagent (a cold saturated solution of picric acid) gives crystalline pale yellow precipitates with many alkaloids.

Gallotannin (a freshly prepared solution) gives white or cream-coloured precipitates with most alkaloidal salts in neutral solution.

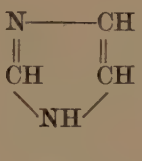
Chemical classification of alkaloids.—Alkaloids are frequently classified according to their chemical constitution, but such a system of classification is not, in our present state

[1] Nelson and Leonard, *J. Amer. Chem. Soc.*, 1922, **44**, 369.
[2] See also Cappelli, *Annali Chim. Appl.*, 1924, **14**, 261.

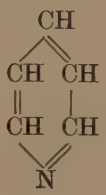
of knowledge, entirely satisfactory. It may, however, be pointed out that all naturally occurring alkaloids contain one or more heterocyclic (carbon-nitrogen) rings, and most of them contain the carbon-nitrogen skeleton of one or other of the following simple heterocyclic bases :—



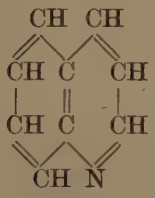
Pyrrole



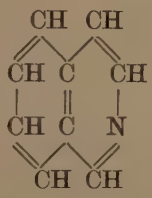
Glyoxaline



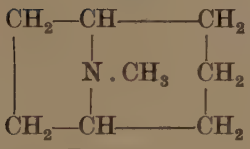
Pyridine



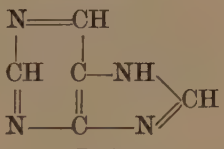
Quinoline



Iso-quinoline

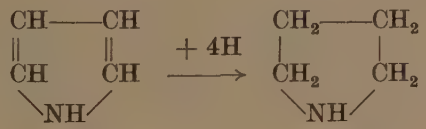


Tropane



Purine

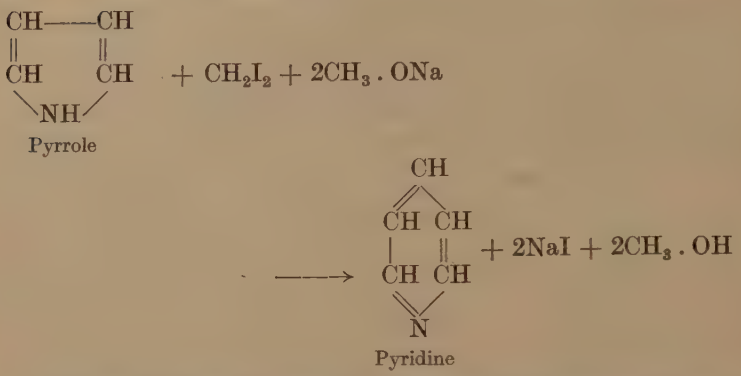
Pyrrole occurs in coal tar and in bone oil, and is a liquid with feeble basic properties. On reduction it yields pyrrolidine, a saturated compound which is a strong secondary base :—



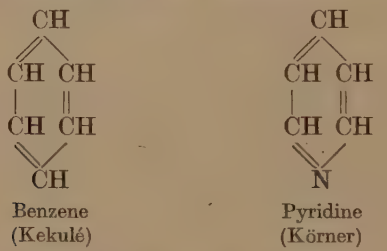
Pyrrole Pyrrolidine

A remarkable reaction occurs when pyrrole reacts with methylene di-iodide and sodium methoxide, the five-membered ring opening and absorbing a carbon atom, with formation of pyridine.[1]

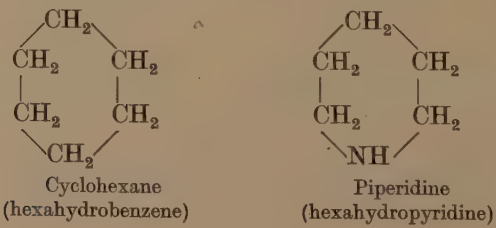
[1] Dennstedt and Zimmermann, *Ber.*, 1885, **18**, 3316.



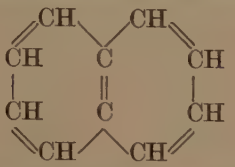
Pyridine is closely related in structure to benzene, from which it differs in that it contains a nitrogen atom in place of a $\rangle$CH group of the ring. The problem of the structure of pyridine is similar to that of benzene, in that the exact disposition of the fourth valency bonds of the carbon atoms, and the third valency bond of the nitrogen atom, is unknown. The formula given above is that of Körner, and corresponds exactly with Kekulé's benzene formula :—



On reduction, the tertiary base pyridine is converted into a secondary base, piperidine, a compound which bears the same relationship to pyridine as cyclohexane does to benzene :—



Quinoline and *iso-quinoline* are related to naphthalene,



in very much the same way that pyridine is related to benzene.

On the basis of the ring structures they contain, the more important plant alkaloids may be classified as follows :—

Pyridine group: Coniine, pelletierine, arecoline, piperine, trigonelline.

Tropane group: Hyoscyamine, atropine, hyoscine, cocaine.

Quinoline group: Quinine, quinidine, cinchonine, cinchonidine, strychnine, brucine.

Iso-quinoline group: Hydrastine, berberine, narcotine, papaverine.

Glyoxaline group: Pilocarpine.

Purine group: Xanthine, theobromine, caffeine.

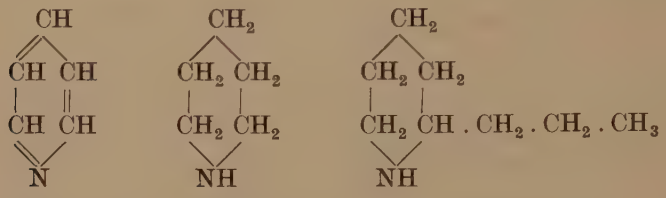
Some common alkaloids (such as morphine, codeine, and thebaine) do not fall satisfactorily into any of these classes, and others (the alkaloids of ergot, for example) are, at present, of unknown constitution.

It is an interesting and important, though not surprising, fact that the different alkaloids present in any particular plant are nearly always closely related in structure, and in the following pages the more important individual alkaloids will be described under the medicinal plants in which they occur. As far as possible, the plants have been arranged in such an order as to keep together those alkaloids which are closely related to one another. Thus the plants dealt with first are those containing alkaloids which are simple derivatives of pyridine.

Hemlock alkaloids.

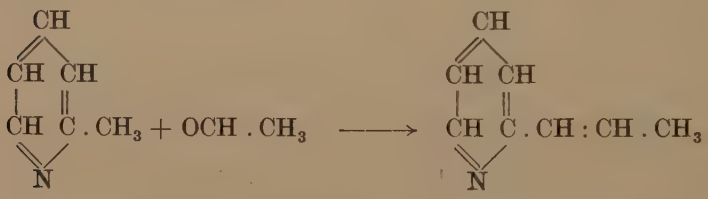
The spotted hemlock (*Conium maculatum*) contains the closely related alkaloids coniine, N-methyl coniine, conhydrine, pseudo-conhydrine, and γ-coniceine. Of these, coniine is the most important, and is present in by far the greatest proportion.

Coniine, $C_8H_{17}N$, is one of a number of alkaloids derived from piperidine, the reduction product of pyridine. Coniine is 2-propyl piperidine, and its relationship to the parent bases will be evident from an inspection of their structural formulæ :—

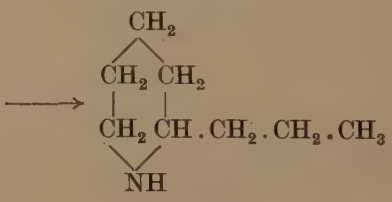


Pyridine Piperidine Coniine

Coniine was synthesised by Ladenburg as long ago as 1886,[1] and was, in fact, the first naturally occurring alkaloid to be prepared artificially. Ladenburg's synthesis consisted in condensing α-picoline (2-methyl pyridine) with acetaldehyde, and reducing the resulting 2-propenyl pyridine with sodium and alcohol :—



α-picoline 2-propenyl pyridine



Coniine

The synthetic product is an optically inactive *dl*-mixture, and from it *d*-coniine, identical with the natural alkaloid, has been obtained by resolution.[2]

The other hemlock alkaloids are all simple piperidine derivatives.

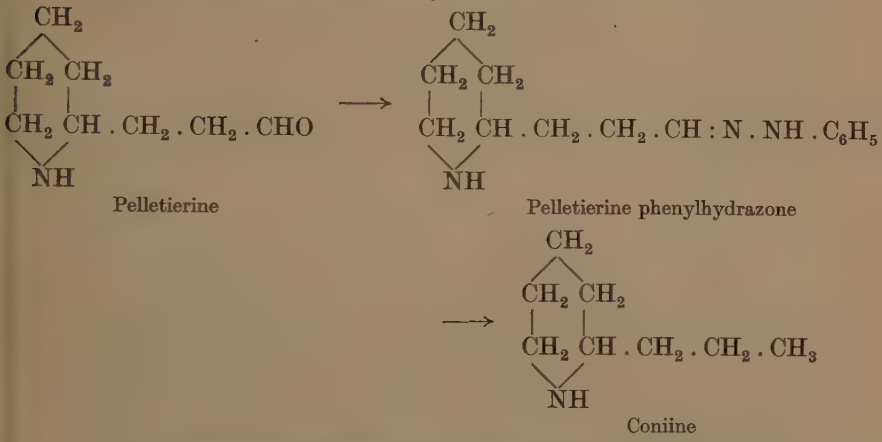
[1] *Ber.*, 1886, **19,** 439 and 2578.

[2] See also *Ber.*, 1906, **39,** 2486.

Pomegranate alkaloids.

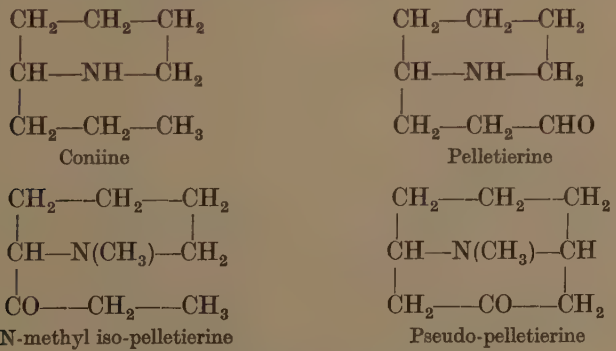
The bark of the root and stem of the pomegranate tree (*Punica Granatum*) contains the alkaloids pelletierine, pseudo-pelletierine, N-methyl iso-pelletierine, and others. These alkaloids are all piperidine derivatives.

Pelletierine, $C_8H_{15}ON$, is an aldehyde derived from coniine. Pelletierine has, in fact, been converted into coniine by reduction of its hydrazone :—



Pelletierine — Pelletierine phenylhydrazone — Coniine

The pomegranate alkaloids have been carefully investigated by Hess and his collaborators,[1] and have been shown to be all closely related to one another and to coniine, in spite of the fact that pseudo-pelletierine contains a dicyclic ring. This relationship is apparent when the formulæ are written in the following way :—



Coniine — Pelletierine

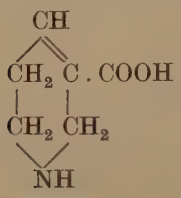
N-methyl iso-pelletierine — Pseudo-pelletierine

[1] Numerous papers in the *Berichte* since 1917.

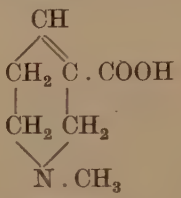
The so-called " pelletierine tannate " of the British Pharmacopœia is a mixture of the tannates of the pomegranate alkaloids.

Areca nut alkaloids.

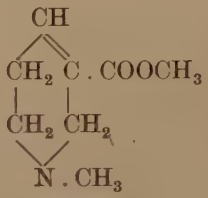
Areca nut (*Areca Catechu*) contains a number of simple alkaloids which are partially reduced pyridine derivatives. The most important of them are :—



Guvacine [1]



Arecaine (N-methyl guvacine)



Arecoline (methyl ester of arecaine)

Of these alkaloids, only *arecoline* has any medicinal importance.

Pepper alkaloid.

Piperine, $C_{17}H_{19}O_3N$, was first isolated from black pepper fruit (*Piper nigrum*), in which it is present to the extent of 5 to 8 per cent. It is also present in smaller proportions in long pepper (*P. officinarum*).

Piperine is hydrolysed by boiling alkalis with formation of piperidine and a complex acid (piperic acid) :—

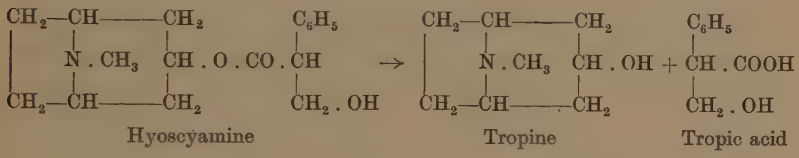
$$\underset{\text{Piperine}}{C_{17}H_{19}O_3N} + H_2O = \underset{\text{Piperidine}}{C_5H_{11}N} + \underset{\text{Piperic acid}}{C_{12}H_{10}O_4}$$

Solanaceous alkaloids.

The drugs obtained from such Solanaceous plants as belladonna, hyoscyamus, stramonium, and datura, owe their action to the presence of a number of closely related alkaloids of comparatively simple structure. These alkaloids, as well as those of the Coca group (*q.v.*), are derivatives of tropine, a compound which is both a tertiary base and a secondary alcohol.

[1] See Freudenberg, *Ber.*, 1918, **51**, 1668.

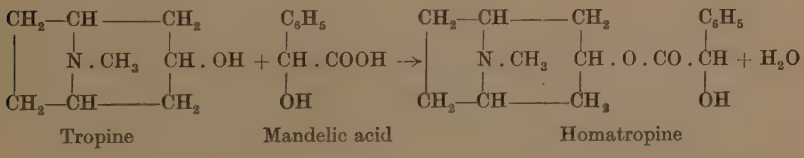
Hyoscyamine, $C_{17}H_{23}O_3N$, one of the simplest of the Solanaceous alkaloids, is an ester derived from tropic acid (the acid) and tropine (the alcohol). It is readily hydrolysed by boiling dilute acids or alkalis :—



Hyoscyamine is a colourless, crystalline compound, and is lævorotatory. It occurs in various Solanaceous plants, such as *Atropa Belladonna*, *Hyoscyamus niger*, and *Datura Stramonium*. When the alkaloid is extracted from any of these plants it usually becomes partly or completely racemised during the process, being thus converted into the corresponding *dl*- compound, which is known as atropine.

Atropine, or *dl*-hyoscyamine, is usually obtained from *Hyoscyamus muticus* or *Scopola carniolica*. It is believed to be not pre-existent in these or in any other plants (except, perhaps, in traces), but to be formed from hyoscyamine during the process of extraction, as previously mentioned. Atropine is a crystalline compound which, for obvious reasons, frequently contains hyoscyamine as impurity.

Homatropine, $C_{16}H_{21}O_3N$, a lower homologue of atropine, is an important synthetic alkaloid prepared by the interaction of tropine and mandelic acid :—



Hyoscine, or **scopolamine,** $C_{17}H_{21}O_4N$, occurs in many Solanaceous plants, notably *Datura fastuosa*, var. *alba*, and *D. Metel*. It is an ester which yields, on hydrolysis, tropic acid and a base known as *oscine* :—

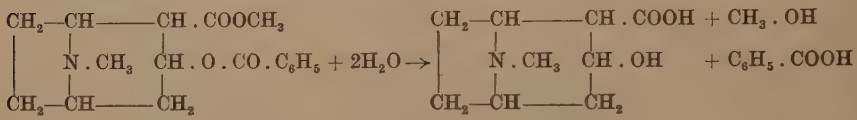
$$C_{17}H_{21}O_4N + H_2O = C_9H_{10}O_2 + C_8H_{13}O_2N$$

Hyoscine — Tropic acid — Oscine

Coca alkaloids.

The most important pharmacological constituent of Coca leaves (species of *Erythroxylum*) is the alkaloid cocaine.

Cocaine, $C_{17}H_{21}O_4N$, is lævorotatory, and crystallises in colourless prisms which dissolve sparingly in water, forming an alkaline solution. It is a derivative of tropine, and is readily hydrolysed by boiling dilute acids or alkalis, with formation of methyl alcohol, benzoic acid, and ecgonine. Ecgonine is a carboxylic acid derived from tropine :—



Cocaine — Ecgonine

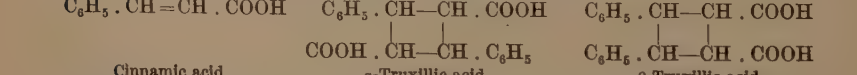
The complete synthesis of cocaine has been effected.[1] The synthetic product is optically inactive, and has been resolved into *d*- and *l*-cocaines by fractional crystallisation of its *d*-or *l*-hydrogen tartrates.

With the exception of cocaine, the only alkaloids of importance present in coca leaves are cinnamyl cocaine, α- and β-truxillines, and tropacocaine. All these alkaloids except tropacocaine are closely related in structure to cocaine itself, and yield ecgonine on hydrolysis. Tropacocaine is a derivative of pseudo-tropine, which is stereoisomeric with tropine. The products of hydrolysis of the coca alkaloids, and their relationships to one another, may be summarised as follows :—

Cocaine	→ ecgonine + methyl alcohol + benzoic acid.
Cinnamyl cocaine	→ ecgonine + methyl alcohol + cinnamic acid.
α- and β-Truxillines	→ ecgonine + methyl alcohol + α- and β-truxillic acids.[2]
Tropacocaine	→ pseudo-tropine + benzoic acid.

[1] Willstätter, Wolfes, and Mäder, *Annalen*, 1923, **434**, 111.

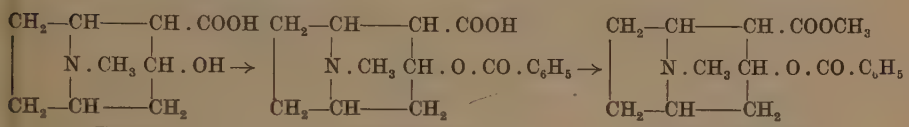
[2] The truxillic acids are isomeric di-cinnamic acids :—



Cinnamic acid — α-Truxillic acid — β-Truxillic acid

A relationship can thus be traced between cinnamyl cocaine and α and β truxillines.

Cocaine forms the greater part of the total alkaloid obtained from Bolivian and Peruvian coca leaves, but the leaves from Java contain cinnamyl cocaine as their principal alkaloidal constituent. Much of the cocaine of commerce is manufactured from cinnamyl cocaine extracted from Javanese coca leaves. The cinnamyl cocaine is boiled with dilute hydrochloric acid, and the ecgonine, isolated from the products of hydrolysis, is first benzoylated, the benzoyl ecgonine being then converted into cocaine by methylation with methyl iodide :—



Tests for cocaine.—1. Dissolve a little cocaine in five or six drops of alcohol. Add two drops of concentrated sulphuric acid and warm, when a pleasant characteristic odour (of methyl and ethyl benzoates) is evolved.

2. The following is a delicate test for benzoic acid, and can be used for the detection of substances like cocaine (which contains a benzoyl group) and atropine (which yields benzoic acid on oxidation).[1] Place a few milligrams of the substance on a watch-glass, add three or four drops of concentrated nitric acid, and evaporate to dryness on a water bath. Add a drop of stannous chloride solution, warm for a minute or two, cool, and add two or three drops of sodium nitrite solution followed by a few drops of a solution of β-naphthol in ammonium hydroxide. A bright orange-red precipitate is obtained. The precipitate is an azo dye formed by the coupling of the β-naphthol with the diazotised amino-benzoic acids.

Cinchona alkaloids.

The barks of the various species of *Cinchona* contain the alkaloids quinine, quinidine, cinchonine, and cinchonidine, and some twenty others of lesser importance. The alkaloids are present in combination with complex acids, such as cinchotannic acid (a phlobatannin) and quinic acid. The percentage of total alkaloids varies considerably in different species of bark, and in this percentage the relative proportions of the different alkaloids is also subject to wide variations. Red cinchona bark of the British Pharmacopœia (*C. succirubra*) is required to contain from 5 to 6 per cent. of total alkaloids, of which not less than one-half should consist of quinine and cinchonidine ; actually, *C. succirubra*

[1] Guerbet, *Compt. rend.*, 1920, **171**, 40.

is exceptionally rich in cinchonidine, which is often present to the extent of from 3 to 4 per cent. Cinchona of the United States Pharmacopœia is the bark of *C. succirubra*, *C. Ledgeriana*, *C. Calisaya*, and their hybrids with other species of *Cinchona*, and is simply required to contain not less than 5 per cent. of total alkaloids. Of all commercial cinchona barks the richest is that of *C. Ledgeriana*, which contains up to 10 per cent. or more of total alkaloids, the quinine content usually averaging 5 to 8 per cent.

Quinine, $C_{20}H_{24}O_2N_2$, the most important of the cinchona alkaloids from a medicinal standpoint, is principally extracted from the bark of *C. Ledgeriana* and its hybrids.

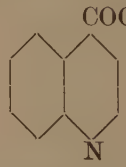
Quinine is a colourless crystalline compound, sparingly soluble in water ; it dissolves easily in ammonia, but is less soluble in solutions of alkali hydroxides than in water. It is a di-acid base, and dissolves freely in excess of dilute hydrochloric and sulphuric acids with formation of the so-called " acid salts," containing two equivalents of the acid. It is remarkable that, although the di-acid salts of quinine are, like most other alkaloidal salts, freely soluble in water, the monacid salts are comparatively sparingly soluble. This is particularly noticeable in the case of the sulphate ; this, the most widely used salt of quinine, is only soluble in water to the extent of about 1 part in 800.

Tests for quinine.—1. A solution in dilute sulphuric acid shows a characteristic blue fluorescence.

2. Dissolve some quinine or a quinine salt in concentrated sulphuric acid in an evaporating dish. Add powdered potassium dichromate, and note the green colour.

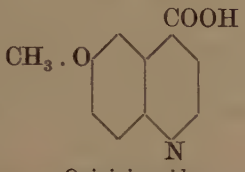
3. To 10 c.cs. of a dilute solution of a quinine salt, add 0·5 c.c. of bromine water, followed by a few drops of ammonia. Note the deep green coloration. This is known as the " thalleioquin test," and is capable of indicating the presence of quinine in a 1 in 20,000 solution.

The cinchona alkaloids are complex derivatives of quinoline (p. 69). Cinchonine and cinchonidine are probably stereoisomeric compounds, and both of them on oxidation yield *cinchoninic acid*, a simple quinoline derivative :—



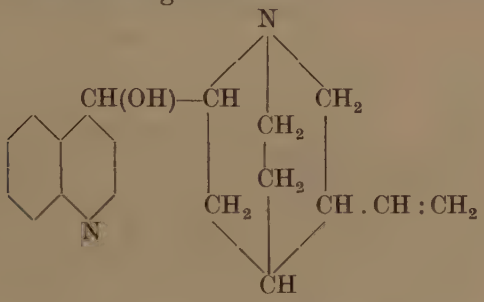
Cinchoninic acid

Quinine and quinidine are also probably stereoisomeric. They differ from cinchonine and cinchonidine in containing a methoxy group (—O . CH_3), and, on oxidation, they yield *quininic acid*:—

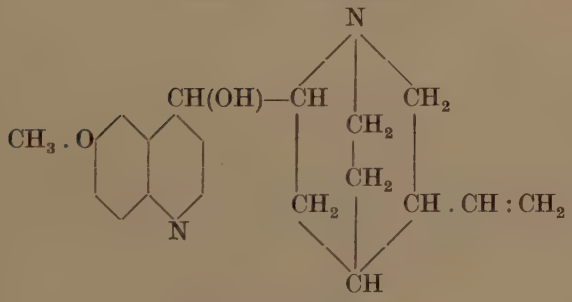


Quininic acid

The following structural formulæ for the cinchona alkaloids were advanced by Königs, and have been amply confirmed by other investigators :—



Cinchonine and cinchonidine



Quinine and quinidine

Strychnos alkaloids.

The two closely related alkaloids, strychnine and brucine, occur in the seeds of various species of *Strychnos*, and are principally extracted from nux vomica seeds and Ignatius beans. These seeds both contain about 2-3 per cent. of total alkaloids, but the relative proportion of strychnine is

usually higher (60-70 per cent.) in Ignatius beans than in nux vomica seeds (about 50 per cent.).

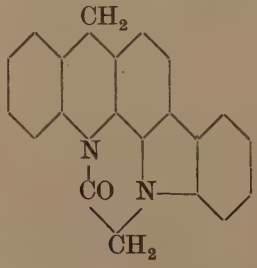
Strychnine, $C_{21}H_{22}O_2N_2$, and **brucine,** $C_{23}H_{26}O_4N_2$, are, like the cinchona alkaloids, complex derivatives of quinoline, as is evident from the fact that strychnine, for example, yields quinoline on fusion with caustic alkalis. It is important to note that, although the strychnine molecule contains two nitrogen atoms, only one of these has basic properties, and consequently strychnine, unlike quinine, forms salts with only one equivalent of an acid.

Brucine differs from strychnine only in that it contains two methoxy groups (—O . CH_3) in place of hydrogen atoms. Brucine is, therapeutically, much less active than strychnine, and, for medicinal purposes, drugs and galenicals prepared from species of *Strychnos* are usually standardised by a determination of the strychnine content rather than the total alkaloid. The method depends upon the fact that, when the mixed alkaloids are warmed with dilute nitric acid, the brucine becomes oxidised to a deep red water-soluble compound, $C_{21}H_{20}O_4N_2$, of the quinone type, whereas the strychnine is not acted upon. The formation of this deep red compound when brucine is treated with nitric acid is commonly employed in the laboratory as a delicate test for nitrate.

Test for strychnine.—Mix a little strychnine with concentrated sulphuric acid in an evaporating dish, and add solid potassium dichromate. Note the evanescent violet colour. This is a very delicate and characteristic reaction.

Test for brucine.—Add concentrated nitric acid, and note the deep red coloration produced.

Strychnine and brucine are very complex alkaloids, but extensive recent investigations by Leuchs and others have thrown considerable light on their structure. Perkin and Robinson have suggested,[1] on the basis of the evidence available, that the molecules of strychnine and brucine contain the following carbon-nitrogen skeleton :—



[1] *Trans. Chem. Soc.*, 1910, **97**, 305.

Opium alkaloids.

Opium is a dried latex prepared from the unripe capsules of the opium poppy (*Papaver somniferum*). About twenty-five alkaloids have been isolated from opium, but many of these occur only in traces, and others are of little medicinal importance. The alkaloids are present in the drug partly as sulphates, and partly in combination with meconic acid, $C_5HO_2(OH)(COOH)_2$. Meconic acid gives an intense red colour with ferric chloride, and this provides a simple and valuable method for the detection of opium.

The most important opium alkaloid, and that usually present in the greatest proportion, is morphine. The percentages of morphine found in different varieties of opium vary considerably, owing to the different conditions under which the plant is cultivated and the drug prepared. Turkey opium contains, as a rule, from 12-16 per cent. or more, Persian opium from 10-12 per cent., and Indian opium from 7-10 per cent., of anhydrous morphine. The only other alkaloids of importance are narcotine, codeine, thebaine, narceine, and papaverine. The narcotine content varies from about 2-9 per cent., and in some samples of opium is actually greater than the morphine content. Codeine is usually present to the extent of 0·1-3·0 per cent.

Turkey opium is the most commonly used variety for medicinal purposes. It is imported in the form of large irregular masses, which have usually been wrapped in poppy leaves, and sprinkled with *Rumex* fruits to prevent them sticking together. Turkey opium is met with in commerce in two distinct forms: "Soft Shipping" opium, which is fairly soft and contains about 30 per cent. of water; and "Druggist's" opium, which is harder and contains about 20 per cent. of water. Of these forms, "Druggist's" opium is most widely used in England for pharmaceutical purposes, "Soft Shipping" being largely employed in the manufacture of morphine. "Druggist's" opium is granular in texture, and so differs from Persian opium, which is prepared by a process which renders it more homogeneous.

The various opium alkaloids produce somewhat different physiological effects, and the therapeutic action of opium, while resembling that of morphine, is necessarily modified by the presence of the other alkaloids.

Morphine, $C_{17}H_{19}O_3N$, was the first alkaloid to be discovered, and was isolated in crystalline form and recognised as a base by Sertürner as long ago as 1806.

Morphine is a crystalline compound, sparingly soluble in water. It is a monacid base, and its molecule contains two hydroxyl groups, one of which is phenolic and the other alcoholic. As a result of the presence of the phenolic hydroxyl group, morphine, unlike most alkaloids, is soluble in solutions of sodium, potassium, and calcium hydroxides with formation of metallic derivatives. This fact is made use of in the British and United States pharmacopœial methods for the estimation of morphine in opium.

Tests for morphine.—1. Note that morphine is freely soluble in aqueous sodium hydroxide, a fact which distinguishes it from most other common alkaloids.

2. Heat a fragment of morphine or a morphine salt with concentrated sulphuric acid on a water bath for 15 minutes, cool, and add a few drops of dilute nitric acid. A violet colour is produced, rapidly changing to blood-red.

3. Add a few drops of ferric chloride and potassium ferricyanide solutions to a solution of a morphine salt and allow to stand, when a Prussian blue precipitate is formed.

4. Morphine liberates iodine from iodic acid. Add a solution of a morphine salt to a cold solution of potassium iodate containing starch mucilage, when blue "starch iodide" is produced.

5. Fröhde's reagent (0·1 gram of ammonium molybdate in 10 c.cs. of concentrated sulphuric acid) gives a violet colour when added to a trace of morphine.

Codeine, $C_{18}H_{21}O_3N$, is the methyl ether of morphine, from which it is usually prepared by methylation. The methyl group displaces the hydrogen atom of the phenolic hydroxyl group of morphine, and codeine is, consequently, incapable of forming metallic salts on treatment with alkali hydroxides.

The principal chemical properties of morphine and codeine, and their relationship to one another, may be summarised in the following way :—

$C_{16}H_{16}ON\begin{cases}CH\,.\,OH\\OH\end{cases}$ Morphine

$C_{16}H_{16}ON\begin{cases}CH\,.\,OH\\O\,.\,CH_3\end{cases}$ Codeine

Apomorphine, $C_{17}H_{17}O_2N$, a compound widely used as an emetic, is prepared from morphine by heating it in sealed tubes at 140° with concentrated hydrochloric acid, when

each molecule of morphine loses one molecule of water. On methylation, apomorphine is converted into *apocodeine*, $C_{18}H_{19}O_2N$.

Diamorphine, or **heroin,** $C_{21}H_{23}O_5N$, is the diacetyl derivative of morphine, from which it is prepared by the action of acetic anhydride :—

$$C_{16}H_{16}ON\begin{cases}CH\,.\,OH\\OH\end{cases} \rightarrow C_{16}H_{16}ON\begin{cases}CH\,.\,O\,.\,CO\,.\,CH_3\\O\,.\,CO\,.\,CH_3\end{cases}$$

Morphine — Diamorphine

Structure of the opium alkaloids.—The alkaloids of opium may be divided into two distinct groups :—

The *isoquinoline group* (including narcotine and papaverine).

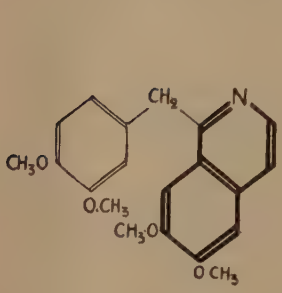
The *morphine group* (including morphine, codeine, and thebaine).

Several alkaloids of the first group have been prepared synthetically, and their structures are well established. On the other hand, the complete structures of the alkaloids of the morphine group cannot be regarded, at present, as being definitely settled, in spite of the immense amount of work which has been done on the subject.[1] It has been definitely shown that morphine and the related alkaloids contain a phenanthrene nucleus,

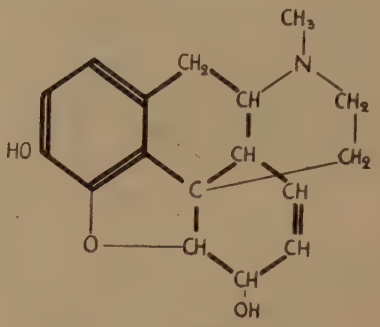
and the various formulæ which have been proposed are based primarily on this fact.

The general relationship between the two groups of opium alkaloids is shown by the formulæ of the following typical substances, in which the isoquinoline or phenanthrene nucleii are indicated by heavy type :—

[1] A valuable summary of the earlier work on the morphine alkaloids is given by Gulland and Robinson, *Trans. Chem. Soc.*, 1923, **125,** 980.



Papaverine [1]



Morphine [2]

Jaborandi alkaloids.

Under the name " jaborandi " the leaves of a number of species of *Pilocarpus* and other plants have been employed in medicine. Originally, Pernambuco leaves (from *P. Jaborandi*) were used, but at the present time the variety principally found in commerce is Maranham jaborandi (from *P. microphyllus*).

Pernambuco leaves contain about 0·7 per cent. of total alkaloids, and Maranham leaves rather more.[3] The most important alkaloidal constituent of jaborandi leaves is pilocarpine, which was isolated in 1875. Other well-authenticated alkaloids which have been isolated are pilocarpidine (from Pernambuco) and iso-pilocarpine and pilosine (from Maranham).

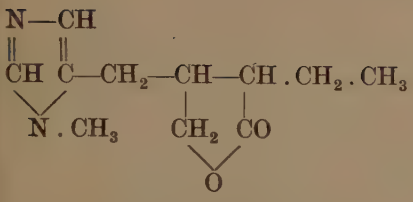
Pilocarpine, $C_{11}H_{16}O_2N_2$, is an oil, or a crystalline solid of low melting-point. Its molecule contains a glyoxaline nucleus, and its structure, and that of pilocarpic acid (of which it is the lactone), have been represented by the following formulæ,[4] which have been confirmed by the more recent work of Pyman and others :—

[1] Synthesised by Pictet and Gams, *Compt. rend.*, 1909, **149,** 210.

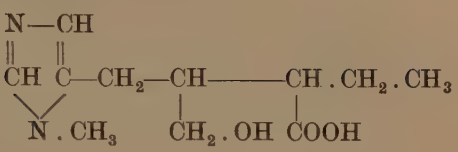
[2] Formula of Gulland and Robinson, *Mem. Manch. Phil. Soc.*, 1925, **69,** No. 10.

[3] Paul and Cownley, *Y.B. Pharm.*, 1897, 140.

[4] Pinner and Schwarz, *Ber.*, 1902, **35,** 2441.



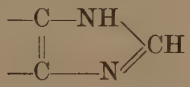
Pilocarpine



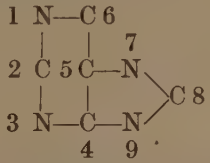
Pilocarpic acid

Purine derivatives.

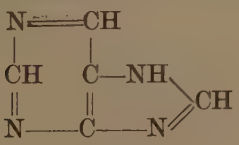
The alkaloids xanthine, theobromine, and caffeine are all derivatives of the simple base purine (p. 69), which itself may be regarded as a glyoxaline derivative, inasmuch as it contains the grouping :—



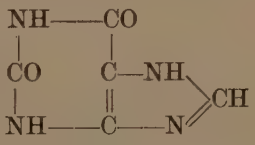
In order to indicate the positions of groups in purine derivatives, the carbon and nitrogen atoms of the purine skeleton are numbered in the following way :—



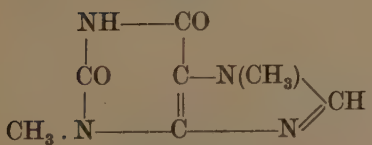
The relationship of xanthine, theobromine, and caffeine to each other and to purine will be seen at once by inspection of their formulæ :—



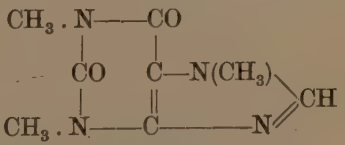
Purine



Xanthine



Theobromine
(3 : 7-dimethyl xanthine)



Caffeine
(1 : 3 : 7-trimethyl xanthine)

Other purine derivatives, particularly uric acid, are important products of animal metabolism, but are outside the scope of this book.

Caffeine, $C_8H_{10}O_2N_4$, occurs in tea leaves, and in the seeds of coffee, guarana, and kola. It is usually obtained by extracting tea dust or sweepings with boiling water, the tannin, etc., present in the decoction being removed by precipitation with litharge or basic lead acetate prior to crystallisation of the caffeine.

Caffeine is a crystalline compound, easily soluble in hot water. It is a very feeble base, and is neutral to litmus. Its salts are freely hydrolysed by water, and, from their aqueous solutions, the free base can be extracted by shaking with organic solvents. A familiar example of the hydrolysis of a caffeine salt is afforded by the citrate, a solution of which, in a little warm water, deposits free caffeine on cooling.

Tests for caffeine.—1. Note that caffeine gives no precipitate with Mayer's reagent.

2. Add a few drops of concentrated nitric acid to a small quantity of caffeine, and evaporate to dryness on a water bath. The residue gives a deep purple colour on addition of ammonia. This is known as the murexide reaction, and is given by all the alkaloids of the purine group, as well as by uric acid and other similar purine derivatives.

Theobromine, $C_7H_8O_2N_4$, is the main alkaloid of cocoa beans, from which it is obtained.

The basic properties of theobromine are even more feeble than those of caffeine, and its salts with acids are very unstable. At the same time, it has the properties of a weak acid, and reacts with metallic hydroxides to form more or less stable salts, the metal displacing the hydrogen atom of the $\rangle NH$ group. The sodium salt, $C_7H_7O_2N_4Na$, is a constituent of the so-called "theobromine and sodium salicylate" or "diuretin."

Xanthine, $C_5H_4O_2N_4$, occurs in small quantities in tea, but is a relatively unimportant alkaloid.

Ergot alkaloids.

Ergot is the sclerotium of a fungus, *Claviceps purpurea*, the spores of which develop in the ovary of the rye. Four

definite alkaloids have been isolated from ergot, and these form two pairs of closely related substances :—

Ergotoxine and ergotinine.
Ergotamine and ergotaminine.

Ergotoxine and ergotinine differ in composition by H_2O, and are intraconvertible by the action of reagents which effect, respectively, the removal or addition of water :—

Warm with acetic anhydride or boil with methyl alcohol.

Ergotoxine $\rightleftarrows$ Ergotinine
$C_{35}H_{41}O_6N_5$ Warm with an alcoholic solution of phosphoric acid. $C_{35}H_{39}O_5N_5$

Ergotamine and ergotaminine are isomeric, and are easily convertible one into the other :—

Ergotamine $\rightleftarrows$ Ergotaminine
$C_{33}H_{35}O_5N_5$ $C_{33}H_{35}O_5N_5$

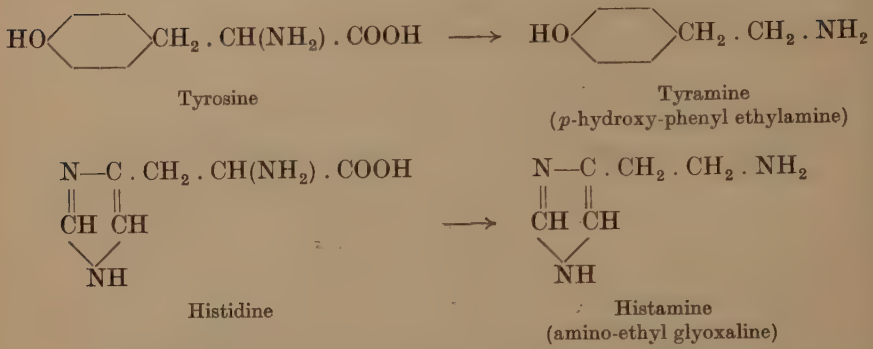
Therapeutically, only **ergotoxine** [1] and **ergotamine** [2] are of importance. These two alkaloids both possess great physiological activity, and they are, as far as is at present known, pharmacologically identical.[3] They differ widely in chemical and physical properties ; ergotamine is crystalline and forms soluble crystalline salts, whereas ergotoxine has only been obtained as an amorphous powder. Both ergotoxine and ergotamine have been put on the market, the former as its phosphate and ethane sulphonate, and the latter as its tartrate.

Other substances present in ergot which affect the uterus and blood pressure are believed to be products of the degradation of protein in the metabolism of the fungus, or to be formed by fermentation or bacterial action in the extracts. The most important of these compounds are two bases, *tyramine* and *histamine*, which are also found in decomposing protein from other sources ; they are formed by the putrefaction of tyrosine and histidine, two amino-acids which are commonly met with as products of protein hydrolysis :—

[1] Barger and Carr, *Trans. Chem. Soc.*, 1907, **91**, 337.

[2] Spiro and Stoll, *Verh. Schweiz. Nat. Ges.*, 1920 ; Stoll, *Schweiz. Apoth. Zeit.*, 1922, **60**, 341.

[3] Dale and Spiro, *Arch. exp. Path. Pharm.*, 1922, **95**, 337.



Extracts of ergot are complex mixtures which may or may not contain varying amounts of the specific alkaloids (ergotoxine and ergotamine). It has been repeatedly shown that liquid extract of ergot of the British Pharmacopœia is prepared in such a way as to render it practically devoid of these alkaloids, and such therapeutic value as it possesses is chiefly due to tyramine and histamine.

Standardisation of ergot preparations.—Adrenalin (p. 134) causes contraction of the isolated rabbit's uterus, but, after previous administration of ergot alkaloids, it produces no effect. A definite concentration of ergot alkaloids is required to produce this result, and the effect can therefore be used to standardise ergot preparations by comparison with one of the specific alkaloids. This method was devised by Broom and Clark,[1] and is now commonly employed in practice.

Aconite alkaloids.

Various plants of the genus *Aconitum* contain alkaloids which are closely related to one another and which are known collectively as the aconitines. The aconitines from different plants are definitely different chemically, and differ considerably in toxicity. Their chemical constitutions are unknown. The various aconitines are distinguished by prefixes, which, in many cases, indicate their sources : thus we have japaconitine (from *A. uncinatum*, var. *japonicum*),

[1] *J. Pharmacol. Exp. Therap.*, 1923, 59. This paper also contains a summary of earlier biochemical methods for the standardisation of ergot preparations. See also Burn and Ellis, *Pharm. J.*, 1927, **118**, 384.

indaconitine (from *A. chasmanthum*), lappaconitine (from *A. septentrionale*), and pseudaconitine (from *A. laciniatum*).

Aconitine.—The simple name aconitine is applied to the alkaloid from *A. Napellus*, which probably has the formula $C_{34}H_{47}O_{11}N$,[1] although $C_{34}H_{45}O_{11}N$ has been proposed.[2] Aconitine is a highly toxic, crystalline substance which on hydrolysis yields, successively, the much less toxic substances *benzoyl aconine* and *aconine*:—

$$\underset{\text{Aconitine}}{C_{34}H_{47}O_{11}N} + H_2O = \underset{\substack{\text{Benzoyl aconine}\\\text{(picraconitine)}}}{C_{32}H_{45}O_{10}N} + \underset{\text{Acetic acid}}{CH_3 . COOH}$$

$$\underset{\text{Benzoyl aconine}}{C_{32}H_{45}O_{10}N} + H_2O = \underset{\text{Aconine}}{C_{25}H_{41}O_9N} + \underset{\text{Benzoic acid}}{C_6H_5 . COOH}$$

Attempts to determine the structure of aconitine have not met with any pronounced success, and it is probable that the substances employed by different investigators have not been identical. Thus, it has been suggested that the alkaloid from English sources is not the same as that from German sources,[3] and, more recently, Merck's aconitine (from *A. Napellus*) has been shown to be a mixture of two isomeric crystalline compounds of the formula $C_{34}H_{47}O_{11}N$.[4]

Japaconitine is a highly toxic, crystalline substance, very similar to aconitine. On hydrolysis, it behaves in a similar way :—

Japaconitine ——→ benzoyl japaconine + acetic acid.
Benzoyl japaconine ——→ japaconine + benzoic acid.

Japaconitine has been given the molecular formula $C_{34}H_{49}O_{11}N$, but more recent work seems to show that it is, like aconitine itself, a mixture of isomerides of the formula $C_{34}H_{47}O_{11}N$.[5]

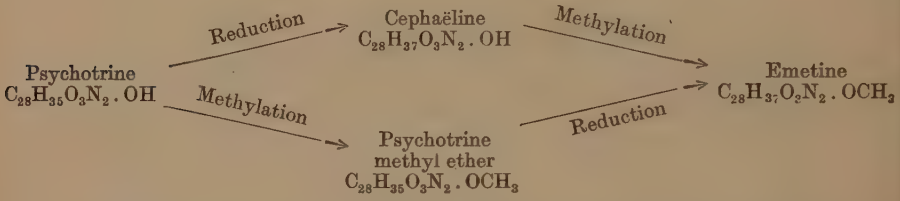
Ipecacuanha alkaloids.

The root of *Psychotria Ipecacuanha* contains about 2·5 per cent. of alkaloids, which are present mainly in the root bark.

[1] Freund and Beck, *Ber.*, 1894, **27,** 433.
[2] Schulze, *Apoth. Zeit.*, 1904, **18,** 783; 1905, **20,** 368.
[3] See Dunstan, *Trans. Chem. Soc.*, 1905, **87,** 1653; and Brady, *Trans. Chem. Soc.*, 1913, **103,** 1821.
[4] Majima and Suginomé, *Ber.*, 1924, **57** (B), 1466.
[5] Majima, Suginomé, and Morio, *Ber.*, 1924, **57** (B), 1456.

Emetine, which constitutes some 70 per cent. of the total alkaloids, has been known for over a hundred years, but was first obtained in the pure state by Paul and Cownley,[1] who also isolated cephaëline and psychotrine. More recently, two other alkaloids, emetamine and psychotrine methyl ether, have been obtained.[2]

The complete structures of the ipecacuanha alkaloids are not known, but their mutual relationships have been investigated by Carr and Pyman.[3] Cephaëline is a reduction product of psychotrine, and emetine is the methyl ether of cephaëline; the relationships between the main alkaloids may therefore be summarised as follows :—



Emetine, on oxidation with potassium permanganate, yields a simple iso-quinoline derivative, and the ipecacuanha alkaloids may therefore be placed in the iso-quinoline group.

Drugs Containing Alkaloids.

Class of Alkaloids.	Drug.	Botanical Source.	Main Alkaloids.
Pyridine derivatives	Areca nuts	*Areca Catechu*	Arecoline, arecaine, guvacine.
	Black pepper	*Piper nigrum*	Piperine (5-8 %).
	Fenugreek seeds	*Trigonella Fœnum-grœcum*	Trigonelline, choline.
	Hemlock fruit	*Conium maculatum*	Coniine (0·5-1·5 %), N-methyl coniine, conhydrine, pseudo-conhydrine, and γ-coniceine.
	Pomegranate bark	*Punica Granatum*	Pelletierine, pseudo-pelletierine, N-methyl iso-pelletierine.

[1] *Pharm. J.*, 1894 (iii.), **25,** 111, 373, and 690.
[2] Pyman, *Trans. Chem. Soc.*, 1917, **111,** 419.
[3] *Trans. Chem. Soc.*, 1914, **105,** 1591.

DRUGS CONTAINING ALKALOIDS.—*Cont.*

Class of Alkaloids.	Drug.	Botanical Source.	Main Alkaloids.
Tropane derivatives	Belladonna leaves and root	*Atropa Belladonna*	Hyoscyamine (0·1-0·7 %).
	Henbane leaves and seeds	*Hyoscyamus niger*	Hyoscyamine (0·05-0·10 %), hyoscine (traces).
	Stramonium leaves and seeds	*Datura Stramonium*	Hyoscyamine (0·2-0·5 %).
	Datura leaves and seeds	*Datura fastuosa*, var. *alba* and *D. Metel*	Hyoscine (0·2-0·5 %).
	Coca leaves	*Erythroxylum Coca*, *E. truxillense* and varieties	Cocaine, cinnamyl-cocaine, α- and β-truxillines, tropacocaine. Total alkaloids, 0·7-2·5 %.
Quinoline derivatives	Red cinchona bark	*Cinchona succirubra*	Quinine, cinchonidine, cinchonine, quinidine. Total alkaloids, 5-6 %.
	Nux vomica seeds	*Strychnos Nux-vomica*	Strychnine, brucine. Total alkaloids, 2-3 %.
	Ignatius beans	*Strychnos Ignatii*	Strychnine, brucine. Total alkaloids, 2-3 %.
Iso-Quinoline derivatives	Berberis stem	*Berberis aristata*	Berberine.
	Bloodroot	*Sanguinaria canadensis*	Sanguinarine, chelerythrine, protopine.
	Calumba root	*Jateorhiza Columba*	Palmatine, jateorhizine.
	Hydrastis rhizome	*Hydrastis canadensis*	Hydrastine (1·5-3·0 %), berberine (3 %), canadine.
	Opium	*Papaver somniferum*	Morphine (7-16 %), narcotine, codeine, thebaine, narceine papaverine.
Glyoxaline derivatives	Jaborandi leaves	Species of *Pilocarpus*	Pilocarpine, isopilocarpine, pilosine (in *P. microphyllus*). Pilocarpine, isopilocarpine (?), pilocarpidine (in *P. Jaborandi*).
Purine derivatives	Cocoa seeds	*Theobroma Cacao*	Theobromine (1-2 %).
	Coffee seeds	*Coffea arabica*	Caffeine (1-1·5 %).
	Guarana	*Paullinia Cupana*	Caffeine (2·5-5·0 %).
	Kola nuts	*Cola vera*	Caffeine (2·5-3·5 %).
	Tea leaves	*Camellia Thea*	Caffeine (1-5 %), theobromine (traces).

DRUGS CONTAINING ALKALOIDS.—*Cont.*

Class of Alkaloids.	Drug.	Botanical Source.	Main Alkaloids.
Alkaloids of unknown or doubtful constitution	Alstonia bark	*Alstonia scholaris* and *A. constricta*	Ditamine, echitenine, ditaine (in *A. scholaris*). Alstonine, porphyrine (in *A. constricta*).
	Aconite root	*Aconitum Napellus*	Aconitine (0·3-0·6 %), picraconitine, aconine. Total alkaloids, 0·5-1·5 %.
	Broom tops	*Cytisus Scoparius*	Sparteine.
	Calabar beans	*Physostigma venenosum*	Physostigmine (eserine). Total alkaloids, 0·1-0·3 %.
	Colchicum corm and seeds	*Colchicum autumnale*	Colchicine (0·2-0·8 %).
	Ergot	*Claviceps purpurea*	Ergotamine, ergotoxine.
	Gelsemium rhizome	*Gelsemium nitidum*	Gelsemine, gelseminine, gelsemoidine
	Ipecacuanha root	*Psychotria Ipecacuanha*	Emetine, cephaeline, psychotrine. Total alkaloids, 2-3%
	Lobelia herb	*Lobelia inflata*	Lobeline, lobelidine.
	Pellitory root	*Anacyclas Pyrethrum*	Pyrethrine (pellitorine).
	Stavesacre seeds	*Delphinium Staphisagria*	Delphinine, delphisine, delphinoidine.
	White hellebore rhizome	*Veratrum album*	Protoveratrine, jervine, rubijervine. Total alkaloids, 0·5-2·0 %.
	Yew leaves, shoots, and fruits	*Taxus baccata*	Taxine.

CHAPTER XII.

ESSENTIAL OILS.

Essential oils are usually secreted as such in plant tissues, but sometimes they are produced from more complex substances by chemical changes brought about subsequent to the collection of the plant. The medicinal action of many drugs is due to the presence of essential oils, but in many cases it is not customary to isolate the oils for medicinal use. Space forbids more than a mention of the oils of betel leaves ; cardamom seeds ; pimento, cummin, fennel, hop, and laurel fruits ; canella, cotton root, oliver, and sassafras barks ; and valerian, orris, and sweet flag rhizomes.

Essential oils differ entirely from fatty oils both in properties and in composition. They can often be distilled without decomposition, and are usually volatile at ordinary temperatures, and do not, therefore, produce a permanent oily mark on paper. They possess characteristic and well-marked odours. The majority of essential oils are liquid at ordinary temperatures, and are characterised by high refractive indices ; most of them are optically active, and the specific rotation is sometimes a valuable diagnostic property.

Chemically, essential oils differ from fatty oils in that they contain no glycerides. They vary considerably in composition, but only in some few cases (such as oil of mustard and oil of wintergreen) do they consist of a single chemical compound in a state of comparative purity.

Most essential oils are volatile in steam without decomposition, and may be obtained from plants containing them by a process of steam distillation, the oil-yielding portion of the plant being extracted by passing a current of steam through it, or by simply boiling it with water. The oily layer is separated from the distillate, and may be subjected

to further processes of purification or rectification. In the case of such essential oils as oil of mustard and oil of bitter almonds, which are produced as a result of enzyme action, the crushed seed must be allowed to stand in contact with water for some time before distillation. Some oils, notably those obtained from various species of *Citrus* (such as oils of lemon, bergamot, and lime), cannot be steam distilled without decomposition, and are usually, therefore, obtained by expression or other mechanical means.

Delicate oils used in perfumery, such as oil of violets, are prepared from the flowers by a process known as "enfleurage." In this process a pure, odourless, fatty substance, such as lard or olive oil, is spread on glass plates and covered with flowers. The flowers, when exhausted, are removed and replaced by fresh ones, and the perfume is finally recovered from the saturated fat by means of alcohol. Alternatively, such oils are sometimes obtained from the flowers by extraction with volatile solvents.

Essential oils are often classified according to the natural orders of the plants in which they occur, but this system has the disadvantage of obscuring the resemblances in composition and properties of various oils. In the following sections the more important essential oils used in pharmacy are classified according to their main chemical constituents, and described under the following groups :—

Oils containing (*as their most important constituents*)—

Hydrocarbons.
Alcohols.
Cineole.
Aldehydes.
Ketones.
Phenols and phenolic ethers.
Esters.

In each section, a description of the individual oils is prefaced by a brief general survey of the more important chemical compounds occurring in them. It must be understood that such a chemical classification, though useful, is far from perfect, owing to the complex composition of the oils, and the fact that many of them contain a number of widely different chemical compounds as important constituents.

Oils containing hydrocarbons.

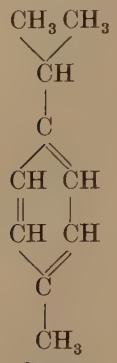
Open chain hydrocarbons, such as those of the paraffin series, are of rare occurrence in essential oils, but have been detected in some few cases.

Most essential oils consist largely of *terpenes*, which are isomeric hydrocarbons of the molecular formula, $C_{10}H_{16}$. Closely related to these are the more complex *sesquiterpenes*, $C_{15}H_{24}$, and *diterpenes*, $C_{20}H_{32}$.

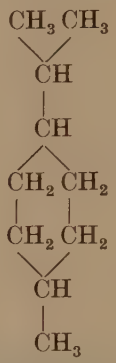
The terpenes are not as a rule highly odorous compounds, and the characteristic odour of most essential oils depends on the presence of oxygen compounds, such as alcohols, aldehydes, ketones, and esters, which may be present only in small proportions, the bulk of the oil being composed of hydrocarbons. Thus oil of lemon contains some 94 per cent. of terpenes, although its characteristic odour is mainly due to the presence of a small proportion (about 4 per cent.) of the aldehyde citral. In some such cases, the greater proportion of the terpenes can be removed by careful fractional distillation under diminished pressure, the residue being a highly concentrated or so-called " terpeneless " oil. Terpeneless oils have two important advantages over the unfractionated product : they are much more readily soluble in alcohol, and they can be stored without appreciable deterioration, whereas ordinary oils frequently develop an unpleasant odour or taste on keeping, owing to oxidation or resinificaton of the terpenes present.

Most of the simple, or *monocyclic*, terpenes are closely related to the aromatic hydrocarbon cymene (*p*-methyl isopropyl benzene),[1] from which they differ in that the six-carbon ring is partly hydrogenated, and has, therefore, no benzenoid character. This relationship will be evident from a comparison of the formulæ of cymene and hexahydrocymene with those of the more common monocyclic terpenes :—

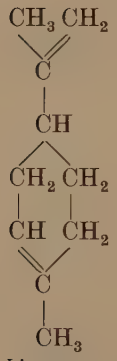
[1] There is good reason for believing that all naturally occurring monocyclic terpenes are derivatives of cymene. The reported natural occurrence of sylvestrene, a terpene derived from *m*-methyl isopropyl benzene, has recently been disproved (Rao and Simonsen, *Trans. Chem. Soc.*, 1925, **127,** 2494).



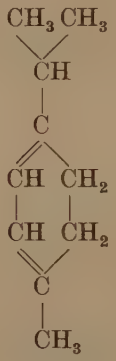
Cymene



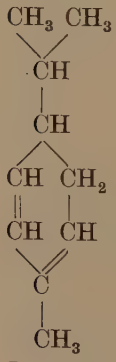
Hexahydrocymene
(fully hydrogenated ring)



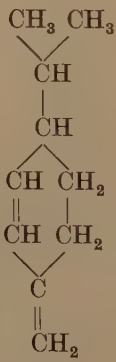
Limonene
(Dipentene)



α-Terpinene

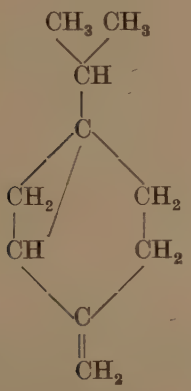


α-Phellandrene

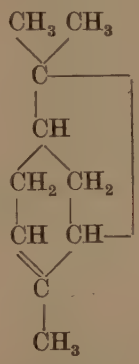


β-Phellandrene

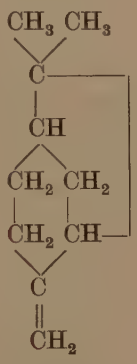
In the more complex *dicyclic* terpenes there is a linkage between non-adjacent carbon atoms of the six-carbon ring, or, as is more usual, the central carbon atom of the iso-propyl group is joined to a carbon atom of the six-carbon ring, forming what is known as a " bridge " :—



Sabinene



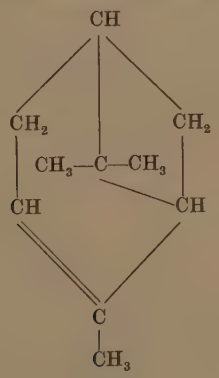
Pinene [1]
(α-Pinene)



β-Pinene

Limonene is a typical terpene. Its molecule contains an asymmetric carbon atom, and it occurs in various essential

[1] The structural formulæ of the dicyclic terpenes and their derivatives are sometimes written in a slightly different way. Compare, for instance, the following representation of the formula of pinene with that given above :—



Pinene

7

oils in the *d*- or *l*- forms, or as a *dl*- mixture. The *dl*- mixture is usually known as dipentene, and is formed when either of the active forms is racemised by heating in sealed tubes at 250°.

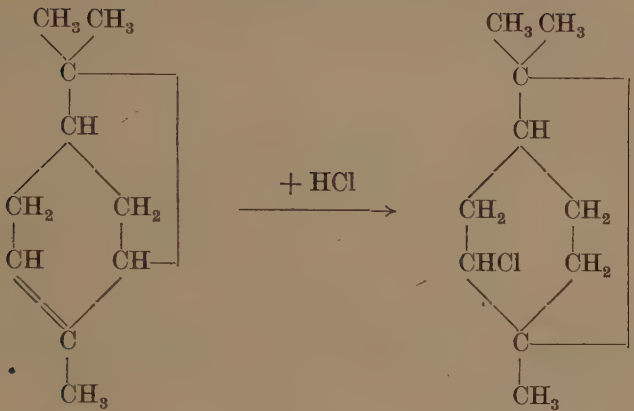
Limonene is a colourless, volatile liquid with a pleasant odour, and boils at 175°. Chemically, it has the typical properties of a di-olefine ; thus, it combines directly with hydrogen chloride to form a di-hydrochloride, $C_{10}H_{18}Cl_2$, and with bromine to form a tetrabromide, $C_{10}H_{16}Br_4$.

Limonene readily undergoes isomeric change, and is converted by alcoholic sulphuric acid, for example, into the more stable hydrocarbon terpinene. Mild oxidising agents convert it into cymene, a reaction which is evidence of the close relationship between the two hydrocarbons.

Pinene is by far the commonest and most widely distributed of the terpenes. It is a colourless liquid, with a characteristic odour of turpentine, and boils at 155°. An inspection of its formula will show that the molecule contains two asymmetric carbon atoms, and both *d*- and *l*- forms occur in nature.

In common with many other terpenes, pinene is very susceptible to the action of oxidising agents, and absorbs oxygen from the air, with formation of complex resinous products—a fact of the greatest practical importance in dealing with essential oils.

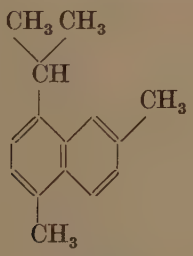
Unlike limonene, pinene contains only one double bond, and therefore combines with only one molecule of a halogen or halogen acid. The reaction does not always result in a simple addition to the double bond ; the combination of pinene with hydrogen chloride (at ordinary temperatures), for instance, involves a remarkable isomeric change, in which the bridged linkage migrates to a different carbon atom of the six-carbon ring, with formation of a compound known as *bornyl chloride*:—



Pinene — Bornyl chloride

Like many other terpenes, pinene readily undergoes isomeric change, and is converted by cold sulphuric acid into dipentene (*dl*-limonene). Dipentene is therefore the principal constituent of the medicinal substance *terebene*, which is prepared from oil of turpentine by shaking it with successive quantities of sulphuric acid until almost optically inactive.

Our knowledge of the structures of the *sesquiterpenes* is largely due to the recent work of Ruzicka and his collaborators.[1] The basis of the sesquiterpene group is the naphthalene nucleus, and many sesquiterpenes are related to the naphthalene derivative, *cadalene*, in much the same way that the simple monocyclic terpenes are related to cymene :—



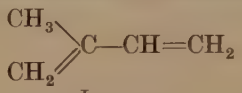
Cadalene

Among the more important well-recognised sesquiterpenes may be mentioned cadinene (from oils of cade and cubebs),

[1] Various papers in the *Helv. Chim. Acta* since 1921.

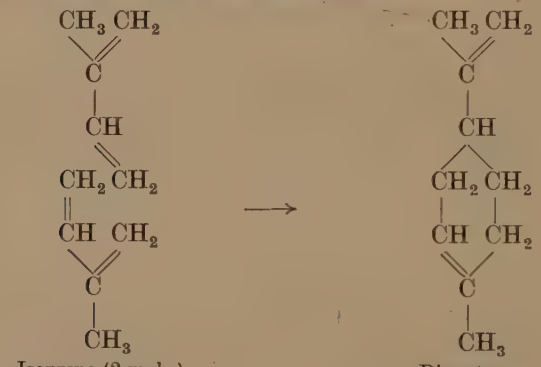
the caryophyllenes (from cloves and copaiba), α- and β-santalenes (from sandal wood oil), and zingiberene (from ginger oil).

The current theory of the natural formation of terpenes and sesquiterpenes is that they are produced by polymerisation of the simple unsaturated hydrocarbon *isoprene*:—

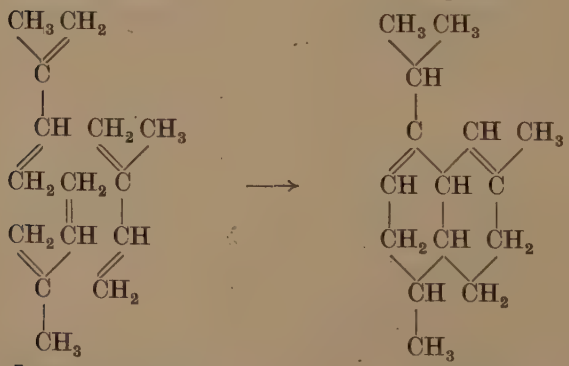


Isoprene

The way in which a typical terpene (dipentene) and a typical sesquiterpene (α-cadinene) are built up from isoprene units may be illustrated in the following way :—



Isoprene (2 mols.) → Dipentene



Isoprene (3 mols.) → α-Cadinene

Oil of turpentine is obtained by distilling the crude oleoresin turpentine (from species of *Pinus*) with water or steam.

The so-called " rectified oil of turpentine " is produced from the crude oil by addition of aqueous sodium hydroxide to neutralise the acids present, and subsequent distillation.

The oils obtained from different species of *Pinus* differ somewhat in composition, but all usually consist chiefly of *d*- and *l*-pinene. The *d*- form predominates in the American oil, making it dextrorotatory, and the *l*- form in the French, making it lævorotatory. Both varieties of oil contain some *l*-*β*-pinene, with smaller quantities of other terpenes and resinous oxidation products.

Oil of juniper is largely distilled in Hungary from ripe juniper berries (*Juniperus communis*).

The oil consists principally of pinene and the sesquiterpene cadinene, but these do not account for its characteristic flavour, which is, no doubt, partly due to oxygenated terpene derivatives. One of the latter, probably a terpene alcohol, is known as juniper camphor.

The so-called " juniper-wood oil " is usually a factitious mixture of the berry oil with turpentine. It is sometimes made by distilling turpentine over juniper berries or over the berries and twigs.

Oil of cubebs is produced from cubeb fruits (*Piper Cubeba*) by steam distillation, the yield being from 10 to 15 per cent.

The composition of this oil is very imperfectly known. It appears to consist largely of unidentified sesquiterpenes, with smaller quantities of terpenes. " Cubeb camphor," found in oil distilled from old cubebs, is not a normal constituent, and is probably produced from a sesquiterpene by oxidation. It appears to be an alcohol of the formula $C_{15}H_{25}$. OH. The cause of the greenish-blue colour of the oil is not definitely known.

Oil of copaiba is obtained by distillation from oleo-resins collected, principally in South America, from species of *Copaifera*. Commercial varieties of the oleo-resin are usually named after Maracaibo, Para, and Maranham, the ports from which they are exported. These copaibas differ considerably from one another in physical properties and in the amount of volatile oil they yield on distillation.

Maracaibo copaiba is typical of the copaibas used in medicine. It yields about 42-53 per cent. of volatile oil, which is lævorotatory, has a specific gravity of 0·896 to 0·910, and boils at 250°-275°. Para copaiba contains more

volatile oil (about 55-90 per cent.) than Maracaibo. A copaiba obtained from West Africa contains about 40 per cent. of oil, which differs from the South American oils, and may be distinguished by the fact that it is dextrorotatory.

Oil of copaiba consists chiefly of sesquiterpenes, among which may be mentioned the isomeric α- and β-caryophyllenes.

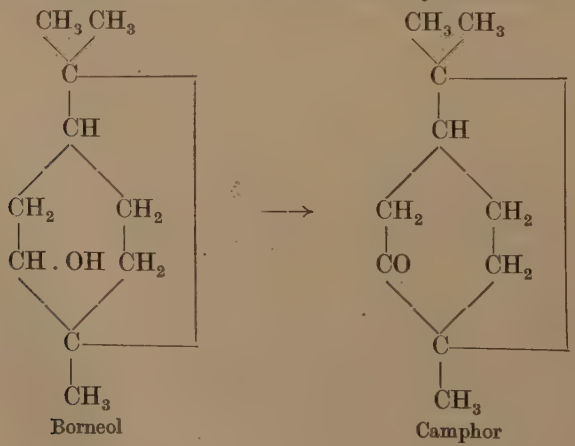
Oil of cade is prepared in South-East France and in Spain, from the wood of *Juniperus Oxycedrus*, by various processes of destructive distillation.

More than 70 per cent. of the oil appears to consist of sesquiterpenes. The sesquiterpene present in the greatest proportion distils between 250° and 260°, whilst another, cadinene (forming about 20-30 per cent. of the oil), distils between 272° and 275°. About 5 per cent. of phenolic substances (guaiacol, ethyl guaiacol, propyl guaiacol), and small quantities of acids, are also present. The latter should not exceed 1·5 per cent. when determined as acetic acid.

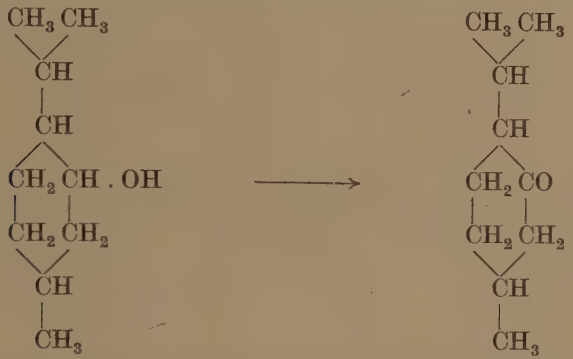
Oils containing alcohols.

Many of the simple aliphatic and aromatic alcohols occur in essential oils in the form of esters. Most of the important alcohols found in oils in the free state are derivatives of, or closely related to, the terpenes.

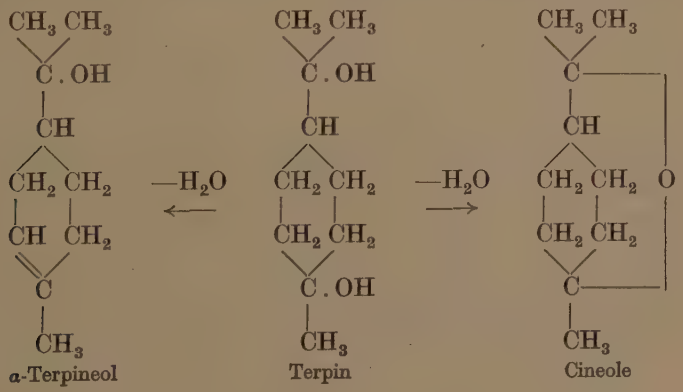
Borneol is a secondary alcohol closely related to bornyl chloride (*q.v.*). It is a crystalline compound which sublimes readily, melts at 204°, and has an odour resembling that of camphor. Camphor itself is the ketone corresponding to borneol, and is formed from the latter by oxidation :—



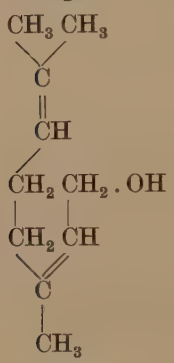
Menthol is a saturated secondary alcohol derived from hexahydrocymene (*q.v.*). It is a colourless, volatile, crystalline compound, with a characteristic odour. On oxidation it yields the corresponding ketone, menthone, which is a liquid :—

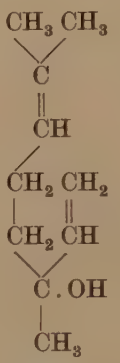


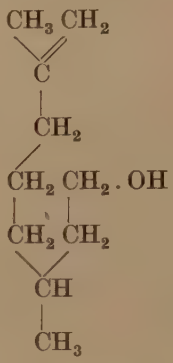
Terpin, a dihydroxy derivative of hexahydrocymene, is a synthetic product of some importance, since its hydrate is used in medicine. Terpin hydrate is a crystalline powder prepared by adding pinene or limonene to a mixture of alcohol and nitric acid, when reactions take place which result in the combination of the hydrocarbon with water. Terpin (or its hydrate) readily loses water on treatment with dehydrating agents, yielding either *terpineol* (an unsaturated tertiary alcohol) or *cineole* (a saturated compound of the ether type), according to the conditions employed. Both terpineol and cineole are of common occurrence in essential oils :—



Many naturally occurring alcohols belong to the class of "open chain" terpene derivatives, so-called from the fact that they contain the typical terpene carbon skeleton, except that the six-carbon ring is broken at one point. Among the more important of these alcohols are the following :—


Geraniol


Linalol


Citronellol

All these compounds contain asymmetric carbon atoms, and exist in optically isomeric forms. The *d*-form of linalol is sometimes known as *coriandrol*, from its occurrence in oil of coriander. *Nerol*, which occurs in oil of neroli, is probably a stereoisomer of geraniol.

"Sesquiterpene alcohols" are, as the same implies, closely related to the sesquiterpenes, and are of fairly common occurrence in oils. They are compounds of high boiling-point, and are frequently crystalline solids. Of the better-known sesquiterpene alcohols may be mentioned the isomeric *santalols*, $C_{15}H_{23}$. OH, of sandal-wood oil.

Determination of alcohols.—The percentage of total alcohols in an essential oil is determined by a process which involves the conversion of the alcohols into their acetates, which are subsequently hydrolysed with standard alcoholic potassium hydroxide. The best form of apparatus for the acetylation process is a flask with a ground-in reflux condenser (an acetylation flask). The total alcohols are calculated together as the equivalent percentage of that alcohol which is present in the greatest proportion. Thus the alcohols in oil of rosemary are calculated together as borneol.

Heat 10 c.cs. of oil of rosemary with 10 c.cs. of acetic anhydride and 2 grams of anhydrous sodium acetate in an acetylation flask for 2 hours. Add water, transfer to a separating funnel, and wash the oily layer, by shaking well with several successive quantities of water, until the washings are no longer acid. Dry the acetylated oil by adding anhydrous sodium sulphate, shaking well, and

allowing to stand. Filter, and treat a weighed quantity (2-5 grams) of the acetylated oil by the process for the determination of esters (p. 117). Calculate the esters in the acetylated oil as bornyl acetate, and hence calculate the percentage of borneol in the original oil.

Example.—The acetylated oil of rosemary was found to contain 13·6 per cent. of esters, calculated as bornyl acetate, $CH_3 . COOC_{10}H_{17}$.

Now, $$\frac{C_{10}H_{17} . OH}{CH_3 . COOC_{10}H_{17}} = \frac{154}{196}$$

$\therefore$ Percentage of alcohols in original oil (calculated as borneol) $= \frac{13{\cdot}6 \times 154}{196}$

$= 10{\cdot}7$ per cent.

It should be noted that this method gives the total alcohols, free and combined (i.e. the result includes the borneol present in the original oil as esters, mainly bornyl acetate). If it is required to determine the free alcohol only, the percentage of esters in the original oil must be estimated as bornyl acetate (as described on p. 117), and this percentage must be subtracted from the 13·6 before multiplying by the factor $\frac{154}{196}$.

Oil of rosemary is obtained from the flowering tops of the rosemary (*Rosmarinus officinalis*), which is largely grown in France and Spain.

The constituents of oils distilled from rosemary are not completely known, but the more important appear to be borneol (10-16 per cent.), bornyl acetate (2-5 per cent.), camphor (17 per cent.), and cineole (about 20 per cent.), the remainder consisting principally of terpenes (pinene and camphene).

Oils of peppermint are produced in Europe and America by the distillation of the herb *Mentha piperita* and its varieties. Japanese peppermint oil is obtained from *Mentha arvensis*.

The chief constituents of peppermint oils are *l*-menthol and its esters (menthyl acetate and menthyl isovalerianate). A genuine oil should contain at least 50 per cent. of alcohols and 5 per cent. of esters. The distinctive odours and tastes of the English, American, and Japanese oils are due to small and variable amounts of other substances, of which may be mentioned aldehydes (acetic and isovalerianic), terpenes (pinene, limonene, phellandrene), esters, and a ketone (*l*-menthone). The Japanese oil also contains the ketone piperitone.

Menthol is very largely obtained from the Japanese oil, in which it is present to the extent of about 80 per cent.

English oil contains 60-70 per cent. of menthol, and the American oil, as a rule, rather less. Menthol may be separated from the oils by freezing.

Oil of coriander is obtained by distillation from the ripe fruits of *Coriandrum sativum*, which contain 0·2-1·0 per cent.

Coriandrol (*d*-linalol), together with small quantities of geraniol and borneol, forms 45-70 per cent. of the oil. Hydrocarbons (chiefly pinene and terpinene) are present to the extent of about 20 per cent.

Oil of lavender is obtained from the flowers of *Lavandula vera* by distillation, either with water or with dry steam. The latter process would seem to be preferable, as the slower distillation with water tends to bring about the hydrolysis of an undue proportion of the esters present in the oil.

French oil of lavender consists principally of linalol, together with 25 to 45 per cent. or more of linalyl acetate, and some 20 per cent. of cineole. The oil is often evaluated on its ester content, but too much importance should not be attached to this, as English oil of lavender commands a much higher price than the French oil, although its ester content is comparatively low (7 to 11 per cent. of linalyl acetate). The distinctive odour of the English oil is, no doubt, partly due to its high cineole content (20 to 30 per cent.).

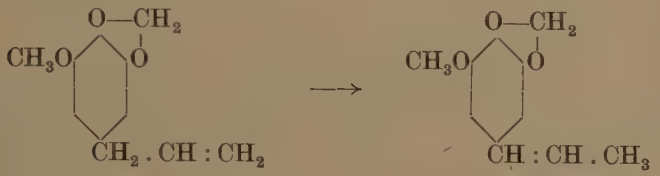
Oil of rose, or otto of roses, is obtained from the fresh flowers of *Rosa damascena*, *R. centifolia*, *R. alba*, and other varieties of rose, cultivated in Bulgaria, France, Persia, Egypt, and India, and is extracted by distillation or by means of solvents.

The solid portion of otto of roses, often known as "stearoptene," consists of hydrocarbons. The liquid portion contains upwards of 70 per cent. of alcohols (chiefly geraniol and citronellol) with small quantities of esters, free acids, eugenol, and aldehydes (nonyl aldehyde and citral).

Oil of nutmegs.—The seeds of the nutmeg tree (*Myristica fragrans*) yield on distillation from 7 to 12 per cent. of volatile oil.

Although the oil consists principally of terpenes (camphene, pinene, and dipentene), the characteristic odour and taste are due to oxygenated compounds, chiefly alcohols (α-terpineol, geraniol, and *d*-borneol), with smaller quantities of the phenolic ether safrole, and phenols (eugenol and iso-

eugenol). The toxicity of the oil is due to a liquid substance, *myristicin*, which is easily converted into a crystalline isomer (melting-point, 45°) :—



Myristicin Iso-myristicin

Oil of sandal wood is distilled from the heart wood of *Santalum album*, a small evergreen tree which is chiefly cultivated in Southern India.

The oil contains two sesquiterpene alcohols (α- and β-santalols) which together form from 92 to 98 per cent. of the oil. Other constituents are small quantities of sesquiterpenes (α- and β-santalenes), aldehydes, ketones, acids, and a low boiling-point hydrocarbon (santene).

West Australian sandal-wood oil is obtained from the plant formerly known as *Fusanus spicatus*. There is some doubt as to the generic status of the plant, but the Bulletin of Miscellaneous Information of the Royal Botanic Gardens, Kew,[1] includes it in the genus *Eucarya*. The oil has been said to consist largely of α- and β-fusanols, two sesquiterpene alcohols which are isomeric with the santalols,[2] but doubt has recently been cast on this work.[3]

Oils containing cineole.

Cineole, or cineol, sometimes known as *eucalyptol* or *cajuputol*, has been mentioned previously as a dehydration product of terpin (*q.v.*). It is a colourless liquid with a camphor-like odour, and behaves chemically like a fairly stable ether.

Estimation of cineole.—Cineole combines with acids (phosphoric, arsenic, hydrochloric, etc.) to form loose compounds which are easily decomposed when treated with

[1] No. 5, 1927.

[2] Rao and Sudborough, *J. Ind. Inst. Sci.*, 1923, **5**, 163. See also Finnemore, *Pharm. J.*, 1925, **115**, 168.

[3] May, *Chemist and Druggist*, 1928, **108**, 42. Compare Parry, *Chemist and Druggist*, 1927, **107**, 710; 1928, **108**, 81.

water. This fact is commonly made use of in the estimation of cineole in essential oils.

The phosphoric acid process.—Cool 10 c.cs. of oil of eucalyptus in a beaker in a freezing mixture, and gradually add about 4 or 5 c.cs. of syrupy phosphoric acid (S.G., 1·75), mixing well. Press the crystalline mass strongly in calico between filter papers, transfer to a small flask with a graduated neck, and add sufficient warm water to bring the liquid near the top of the graduations. Allow to separate, and measure the volume of the oily layer (cineole). Cineole has a specific gravity of 0·93, and the percentage by weight in the oil may thus be calculated, although it is more commonly expressed as percentage volume in volume. This process is described in the *British Pharmacopœia*, which requires oil of eucalyptus to contain not less than 55 per cent., and oil of cajuput not less than 45 per cent., of cineole by volume.

The above method tends to give low results, and the *cresineol* method is claimed to be more satisfactory. Cocking [1] pointed out that cineole forms a molecular compound with ortho-cresol, which has been termed "cresineol," [2] and he devised a method, based on this fact, for the cryoscopic determination of cineole in oils. Three grams of the previously dried oil are mixed with 1·2 grams of ortho-cresol, and the freezing-point of the mixture is determined. From a previously constructed graph in which freezing-points are plotted against percentages of cineole, the cineole content of the oil may be at once read off. This process is claimed to give a maximum error of only 3 per cent.

Oil of cajuput is obtained by distillation from the leaves of various species of *Melaleuca*, which are principally grown in the East Indies and Northern Australia.

These oils contain from 45 to 55 or more per cent. of cineole, together with hydrocarbons, aldehydes, and terpineol and its esters. The oil when rectified is colourless, but normally it has a green or bluish-green colour, due to the presence of traces of copper from the apparatus used in the extraction process.

Oils of eucalyptus are principally produced in Australia and Tasmania. The trees yielding the oils used in medicine are species of *Eucalyptus*, the oils from which contain a large proportion of cineole, but little or no phellandrene.

The oils from different species differ widely in physical properties and composition. A medicinal oil usually contains

[1] *Y. B. Pharm.*, 1920, 391 and 395; *Perf. Essent. Oil Rec.*, 1921, **12**, 339.
[2] The word "cresineol" has been registered as a trade mark.

more than 55 per cent. by volume of cineole. Other substances of common occurrence in eucalyptus oils are alcohols (geraniol, piperitol), aldehydes (citral, citronellal), a ketone (piperitone), terpenes, and esters.

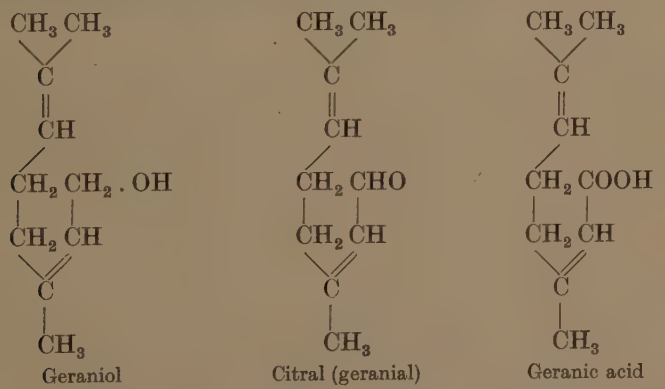
As stated above, the terpene phellandrene is found in certain eucalyptus oils, but its presence in quantity is undesirable in oils intended for medicinal use. When present to the extent of 5 per cent. or more, it may be detected by the formation of its crystalline "nitrite," $C_{10}H_{16}N_2O_3$. The test is usually carried out by stirring together 2 c.cs. of the oil, 4 c.cs. of glacial acetic acid, and 3 c.cs. of a 20 per cent. solution of sodium nitrite.

Oils containing aldehydes.

Benzaldehyde, $C_6H_5 . CHO$, is the product of hydrolysis of the glucosides contained in many plants, and in such cases forms the bulk of the oil obtained by distillation, as in the case of the volatile oil of almonds. These oils have been largely replaced, as flavouring agents, by synthetic benzaldehyde.

Cinnamic aldehyde, $C_6H_5 . CH : CH . CHO$, is the main constituent of oils of cinnamon and cassia.

Citral or *geranial* (present in oils of lemon, lemon-grass, etc.) is the aldehyde corresponding to the alcohol geraniol, from which it is produced on oxidation. Further oxidation of citral results in the formation of geranic acid :—



Geraniol — Citral (geranial) — Geranic acid

Citral is a liquid boiling at 230°, and having a strong odour of lemon. It is of importance both on account of its

flavouring properties and its use as a starting substance for the preparation of compounds ("ionones") widely used in artificial violet perfumes.

Citronellal is the aldehyde corresponding to the alcohol citronellol.

Oil of cinnamon is obtained from the bark of *Cinnamomum zeylanicum*, a tree which is principally grown in Ceylon. The yield of oil is about 0·5-1·0 per cent.

The chief constituents of the oil are cinnamic aldehyde (55-75 per cent.), other aldehydes, the phenol eugenol (4-8 per cent.), and hydrocarbons (phellandrene and caryophyllene).

Cinnamon leaf oil differs from that of the bark in that it contains very little cinnamic aldehyde but much eugenol. Oil of cassia (from *Cinnamomum Cassia*) more closely resembles cinnamon bark oil, but it has a less fragrant odour and a harsher taste. Cassia oil contains from 70-85 per cent. of cinnamic aldehyde, with small amounts of terpenes and other compounds.

Estimation of oil of cinnamon.—The aldehyde content of oil of cinnamon may be determined by conversion of the aldehydes into their bisulphite compounds by shaking with sodium bisulphite solution. A more accurate process consists in shaking the oil with a solution of normal sodium sulphite, when a soluble sulphonate is formed.

The sodium sulphite process.—To 10 c.cs. of oil of cinnamon, contained in a flask with a graduated neck, add 70 c.cs. of a 1 in 5 aqueous solution of sodium sulphite, and sufficient phenolphthalein to give a distinct pink coloration. Heat the mixture on a water bath, shake well, and neutralise with 30 per cent. acetic acid. Repeat the heating and neutralisation until the pink colour fails to return, a process which occupies from 30 to 45 minutes. After allowing to cool, add sufficient sodium sulphite solution to force the oily layer into the neck of the flask, where its volume may be read. This volume, subtracted from 10, gives the volume of aldehydes present in 10 c.cs. of the oil.

A similar process may be applied to oil of lemon-grass. In this case the formation of the soluble sulphonate derived from citral may be represented by the following equation :—

$$C_9H_{15}.CHO + 2Na_2SO_3 + 2H_2O = C_9H_{17}(SO_3Na)_2.CHO + 2NaOH$$

Oil of lemon-grass is distilled from various Graminaceous plants grown in the East and West Indies and in India.

Aldehydes, of which the most important is citral, form about 70-85 per cent. of the oil, the rest consisting of geraniol (4-6 per cent.), geranyl esters, and about 10 per cent. of terpenes (limonene and dipentene).

Oil of lemon is obtained from the fresh peel of *Citrus Medica* var. *β-Limonum*, grown in the countries bordering the Mediterranean.

The oil is extracted from the peel by various mechanical methods. Processes of distillation yield an inferior oil, owing to partial decomposition.

The most important flavouring constituents of oil of lemon are aldehydes (citral, 4-5 per cent., and citronellal) and esters (geranyl acetate, about 1 per cent.). Terpenes (chiefly *d*-limonene), and sesquiterpenes, form, however, about 90 per cent. of the oil.

A terpeneless oil may be obtained by distilling a good lemon oil under diminished pressure until the bulk of the terpenes, and about 2 per cent. of citral, have passed into the distillate. The residue constitutes the terpeneless oil, which contains from 40 to 50 per cent. of citral.

Estimation of oil of lemon.—Owing to the small percentage of aldehydes in oil of lemon, the sodium sulphite process, as used for oils of cinnamon and lemon-grass, cannot be conveniently employed. The following process depends upon the conversion of the aldehydes into their oximes by means of excess of a standard hydroxylamine solution, the excess being then determined by back titration.

The hydroxylamine process.—To 20 grams of the oil, add 20 c.cs. of N/2 hydroxylamine hydrochloride, 20 c.cs. of alcohol, and 8 c.cs. of N/1 alcoholic potassium hydroxide (in order to liberate most of the hydroxylamine from its salt). Boil the mixture under a reflux condenser for 30 minutes, cool, dilute with about 250 c.cs. of water, add phenolphthalein, and run in N/1 alcoholic potassium hydroxide until the liquid just becomes pink. At this point all the excess of hydroxylamine is present in the free state. Add methyl orange, and titrate the hydroxylamine with N/2 sulphuric acid.

Carry out a blank experiment under identical conditions, but omitting the oil of lemon. Calculate the percentage of citral from the difference of the volumes of standard sulphuric acid required in the blank experiment and in the estimation proper.

$$\underset{152}{C_9H_{15}.CHO} + \underset{33}{NH_2.OH} = C_9H_{15}.CH:N.OH + H_2O$$

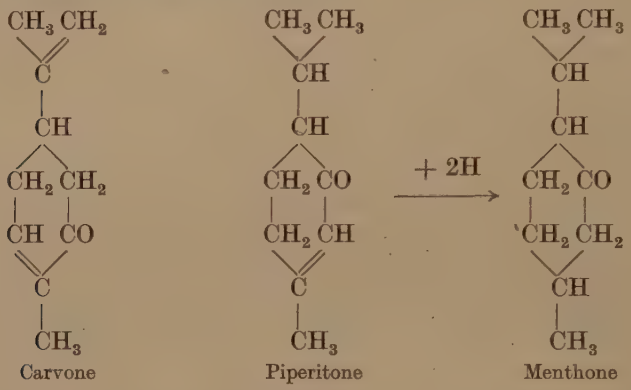
$$\underset{66}{2NH_2.OH} + \underset{98}{H_2SO_4} = (NH_2.OH)_2, H_2SO_4$$

Hence, 1000 c.cs. of N/2 sulphuric acid neutralises 16·5 grams of hydroxylamine, and this is equivalent to 76 grams of citral.

Oils containing ketones.

Many of the higher aliphatic ketones occur in small quantities in oils, but of much more common occurrence are ketones derived from the terpenes.

Carvone, which occurs in many essential oils, and *piperitone*, found in some of the eucalyptus oils, are ketones derived from the monocyclic terpenes. Carvone, it will be noticed, is a simple derivative of limonene. Piperitone is closely related to the saturated ketone *menthone*, into which it can be converted by partial reduction. :—



Camphor, a most important dicyclic terpene derivative, has been previously mentioned. It is obtained from the wood of the camphor tree (*Cinnamomum Camphora*) by steam distillation. From the product, which is a pasty mass, the solid camphor is separated by expression, and is finally purified by sublimation. The residual oil, known as oil of camphor, contains terpenes, phenols, and other compounds, in addition to camphor itself.

Camphor is a colourless, crystalline compound, which melts at 176°, but sublimes freely at temperatures below its melting-point. The natural substance is dextrorotatory, and can be distinguished by this property from synthetic *dl*-camphor, which is manufactured on a considerable scale from pinene. Synthetic camphor appears to be identical in its physiological action with the natural product.[1]

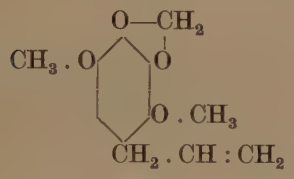
Oil of dill is distilled from the fruits of *Peucedanum graveolens*, which are principally grown in Central and Southern Europe.

European dill fruits yield from 3 to 4 per cent. of oil,

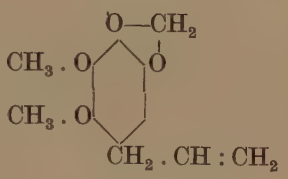
[1] Joachimoglu, *Arch. Exp. Path. Pharm.*, 1920, **88,** 364 ; Gomes da Costa, *Compt. rend. Soc. Biol.*, 1926, **95,** 332.

which contains from 40 to 60 per cent. of *d*-carvone. The rest of the oil consists almost entirely of terpenes (chiefly *d*-limonene).

East Indian and Indian dill oils contain a large percentage of a substance, known as dill-apiole, which has a very high boiling-point (285°), and, unlike any constituent of the European oil, sinks in water. Apiole, which occurs in parsley oil, is isomeric with dill-apiole :—



Apiole



Dill-apiole

Oil of caraway is obtained by distillation from the fruits of *Carum Carvi*, a plant which is largely grown in Holland and in Central and Northern Europe.

Caraway oil consists almost entirely of *d*-carvone (45 to 60 per cent.) and *d*-limonene, with about 1 to 2 per cent. of reduction products of carvone (dihydrocarvone, carveol, and dihydrocarveol).

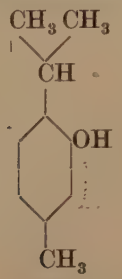
Oil of spearmint is obtained by distillation from the fresh herbs *Mentha viridis* and *M. crispa*, the yield varying from 0·15 to 0·20 per cent. The bulk of the oil in commerce is produced in the Eastern United States, but some is still distilled in Europe.

Oil of spearmint contains 42 to 60 per cent. of *l*-carvone, 6 to 20 per cent. of alcohols, 4 to 20 per cent. of esters, and terpenes (chiefly *l*-limonene). It should be noted that the carvone present in this oil is optically isomeric, and not identical, with the carvone of dill and caraway oils. The characteristic odours of various spearmint oils have been ascribed to the alcohols and esters they contain. Of the alcohols, dihydrocarveol has been found in an American oil, dihydrocuminic alcohol in a German oil, and linalol in a Russian oil.[1]

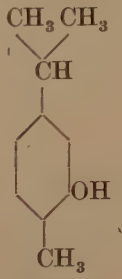
[1] Elze, *Chem. Zeit.*, 1910, **34**, 1175.

Oils containing phenols and phenolic ethers.

Thymol and *carvacrol* are the most important of the simpler phenols found in essential oils. From their structural formulæ it will be seen that they are isomeric compounds derived from cymene :—



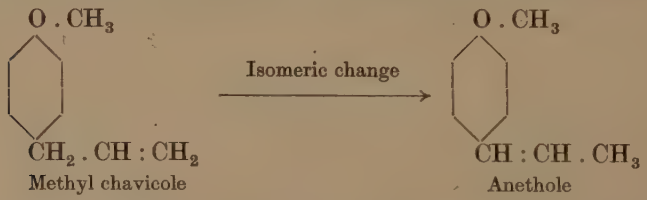
Thymol



Carvacrol

Thymol forms large colourless crystals, but carvacrol is a liquid at ordinary temperatures.

It is interesting to note that a large number of phenols and phenolic ethers found in oils contain an unsaturated side chain, usually $—CH_2 . CH : CH_2$ or $—CH : CH . CH_3$. The side chain $—CH_2 . CH : CH_2$ tends to isomerise, under the influence of reagents, to $—CH : CH . CH_3$. A familiar example is the conversion of methyl chavicole into the isomeric compound anethole by boiling alcoholic potash :—

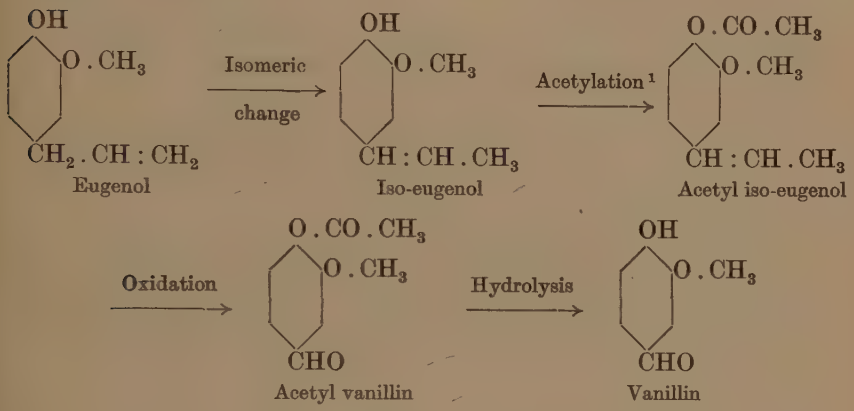


Methyl chavicole — Anethole

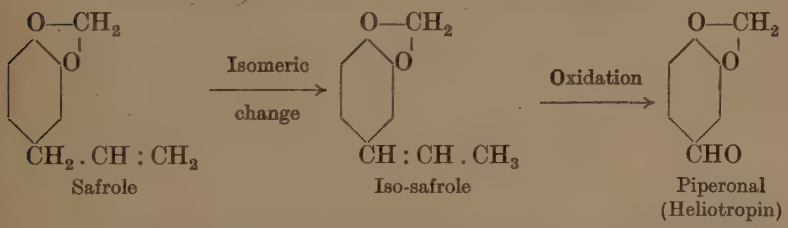
Other examples of this type of isomeric change are the conversion of myristicin into iso-myristicin (p. 107), of eugenol into iso-eugenol, and of safrole into iso-safrole (see below).

Eugenol, a phenol found in oil of cloves, is a particularly important compound on account of its use in the manufacture of artificial vanillin, which has to a considerable extent replaced the natural substance obtained from vanilla pods.

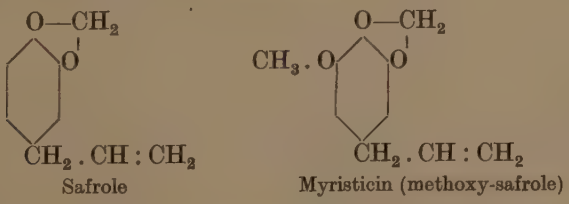
The formation of vanillin from eugenol involves the following series of reactions :—



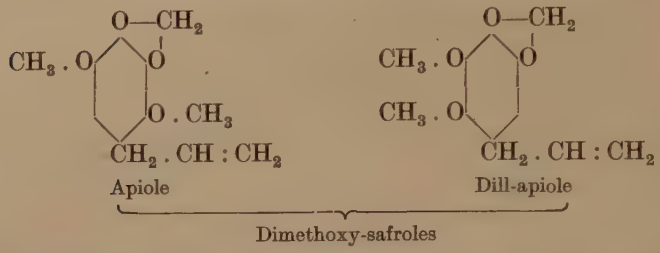
Safrole is a phenolic ether closely related to eugenol, and is used in the manufacture of the aldehyde piperonal (used as a perfume under the name heliotropin) by a series of reactions similar to those used in the preparation of vanillin :—



It may be well to emphasise here the relationship between safrole, myristicin, and the apioles :—



[1] The acetylation process is necessary in order to protect the —OH group during the subsequent oxidation.



Estimation of phenols.—The total phenols in such oils as oil of ajowan and oil of cloves are determined by the following simple process :—

Heat 10 c.cs. of the oil with 100 c.cs. of a 5 per cent. solution of potassium hydroxide, in a flask with a graduated neck, on a water bath. Shake well until the phenols have passed into solution in the alkali, cool, add water to bring the residual oil into the neck of the flask, allow to stand, and measure the oily layer.

Example.—10 c.cs. of oil of ajowan left 5·8 c.cs. of residual oil. The percentage of phenols by volume was, therefore, $(10 - 5{\cdot}8) \times 10$, or 42 per cent.

Oil of ajowan is distilled from the fruits of *Carum copticum*, a plant which is principally grown in India.

The fruits yield from 2 to 4 per cent. of oil, which contains from 35 to 45 per cent. of thymol associated with a small amount of carvacrol. The non-phenolic portion of the oil is sometimes known as " thymene," and consists almost entirely of hydrocarbons (cymene, dipentene, and terpinene).

Oil of cloves is obtained by distillation from the unexpanded flower heads of *Eugenia caryophyllata*. About 90 per cent. of the world's supply of this oil is obtained from the islands of Zanzibar and Pemba, the remainder coming from Sumatra, Penang, and the Seychelles.

Cloves yield from 16 to 19 per cent. of oil, the phenol content of which varies from 84 to 95 per cent. Those oils with the lower phenol content are known in commerce as " opt " and are used in pharmacy, while the " strong " oils may be used for the production of vanillin.

In addition to eugenol, the oil contains about 3 per cent. of acetyl eugenol, together with sesquiterpenes (α- and β-caryophyllenes), esters (methyl benzoate), ketones (methyl *n*-amyl ketone), and alcohols.

Oil of aniseed is obtained by distillation from the fruits of the anise (*Pimpinella Anisum*), and the star anise (*Illicium verum*).

The Pimpinella oil is mostly obtained from Spain, South

Russia, and Bulgaria, the fruits yielding from 1·5 to 3·5 per cent. It contains from 80-90 per cent. of the phenolic ether anethole, and smaller quantities of methyl chavicole and oxidation products (anisic aldehyde, etc.).

The star anise fruits distilled in Southern China yield from 1·7 to 3·5 per cent. of oil, of which rather more than 90 per cent. is anethole. Methyl chavicole is also present, together with oxidation products (anisic aldehyde and acid) and hydrocarbons (*d*-pinene and phellandrene).

Oils containing esters.

The esters of commonest general occurrence in essential oils are the acetates of terpineol, borneol, geraniol, and linalol, all of which are highly odorous substances.

Estimation of esters.—The esters present in essential oils are determined by hydrolysis with standard alcoholic potassium hydroxide and back titration with standard sulphuric acid, a process similar to that employed in the determination of saponification values of fats, fatty oils, and waxes (p. 17).

Most oils contain a number of esters, but these are all calculated together as the equivalent percentage of the ester present in the greatest proportion. Thus, the esters in oil of Siberian fir are calculated as bornyl acetate.

Weigh about 2-3 grams of oil of Siberian fir, dissolve in 25 c.cs. of alcohol, and neutralise the solution, if necessary, with alcoholic potassium hydroxide. Add 25 c.cs. of N/1 alcoholic potassium hydroxide, boil in a flask under reflux for an hour, cool, and titrate the excess of potassium hydroxide with N/1 sulphuric acid, using phenolphthalein as indicator. Carry out a blank experiment under identical conditions, but omitting the oil.

Example.—Weight of oil of Siberian fir = 2·260 grams.

Volume of acid required in estimation proper = 20·4 c.cs.

Volume of acid required in blank experiment = 24·8 c.cs.

∴ Amount of alkali necessary to hydrolyse the esters present is equivalent to 4·4 c.cs. of N/1 acid.

$$\underset{\text{Bornyl acetate}}{CH_3 . COOC_{10}H_{17}} + KOH = CH_3 . COOK + \underset{\text{Borneol}}{C_{10}H_{17} . OH}$$

196

1000 c.cs. of N/1 KOH will hydrolyse 196 grams of bornyl acetate.

∴ 4·4 c.cs. of N/1 KOH will hydrolyse $\frac{196 \times 4{\cdot}4}{1000}$ grams of bornyl acetate.

∴ Percentage of esters (calculated as bornyl acetate) = $\frac{196 \times 4{\cdot}4 \times 100}{1000 \times 2{\cdot}26}$

= 38·2 per cent.

Oil of Siberian fir, or oil of pine, is obtained from the leaves of *Abies sibirica* by distillation. It contains from 30 to 40 per cent. of esters, mainly bornyl acetate. Terpenes

(pinene, camphene, phellandrene, dipentene), sesquiterpenes, and the hydrocarbon santene, C_9H_{14}, have also been detected. Santene is a lower homologue of the terpenes, and has also been found in sandal-wood oil.

Oil of chamomile is obtained by distillation from the flowers of *Anthemis nobilis*, cultivated in Europe and to a less extent in America.

The oil consists mainly of esters of angelic and tiglic acids, two stereoisomeric unsaturated acids of the oleic acid series. The alcohols from which the esters are derived are iso-butyl, amyl, and hexyl alcohols, and an alcohol, anthemol, $C_{10}H_{15}$. OH. The hydrocarbons anthemene and azulene are also present. Azulene is a blue compound, and to it the blue colour of the freshly distilled oil is attributed.

Oil of wintergreen of commerce is obtained by distillation from the leaves of *Gaultheria procumbens* or from the bark of *Betula lenta*. These oils are practically identical in composition, both containing about 99 per cent. of methyl salicylate. The presence of small quantities of other substances modifies the odour slightly.

Oil of mustard does not pre-exist in black mustard seeds (*Brassica sinapioides*), but it is obtained from the cake remaining after expression of the fixed oil, by macerating with water, and subsequently distilling. As mentioned in the chapter dealing with glucosides, the sinigrin undergoes hydrolysis, with formation of allyl iso-thiocyanate, glucose, and potassium hydrogen sulphate.

The oil contains from 92 to 99 per cent. of allyl iso-thiocyanate, together with small quantities of allyl cyanide and carbon disulphide.

Estimation of oil of mustard.—Oil of mustard is estimated volumetrically by an interesting process, depending upon the fact that allyl iso-thiocyanate combines with ammonia to form an additive compound, thiosinamine, which reacts with silver nitrate, in alcoholic ammoniacal solution, to form allyl cyanamide and silver sulphide :—

$$C_3H_5 . N : C : S + NH_3 = \underset{\text{Thiosinamine}}{C_3H_5 . NH . CS . NH_2}$$

$$C_3H_5 . NH . CS . NH_2 + 2AgNO_3 + 2NH_3 = \underset{\text{Allyl cyanamide}}{C_3H_5 . NH . CN} + Ag_2S + 2NH_4 . NO_3$$

In the actual estimation, excess of standard silver nitrate is employed, and the excess is determined, after filtering off the silver sulphide, by titration with ammonium thiocyanate.

Weigh 2 grams of oil of mustard, and dissolve in sufficient alcohol to produce 100 c.cs. Transfer 5 c.cs. of this solution to a flask, add 30 c.cs. of N/10 silver nitrate and 5 c.cs. of dilute ammonia, and heat on a water bath for half an hour, with frequent shaking. Cool, dilute to 100 c.cs. and filter. To 50 c.cs. of the filtrate (representing 0·05 gram of the original oil) add excess of nitric acid, and titrate with N/10 ammonium thiocyanate, using ferric sulphate as indicator.

From the equations given above, it will be seen that $2AgNO_3$ is equivalent to $C_3H_5 . N : C : S$.

Hence, 1000 c.cs. of N/10 $AgNO_3$ is equivalent to 4·95 grams of $C_3H_5 . N : C : S$.

For volatile oil of mustard, the British and United States pharmacopœial requirements are, respectively, 92 per cent. and 93 per cent. of allyl iso-thiocyanate, determined by the above process.

ESSENTIAL OILS CLASSIFIED ACCORDING TO THEIR MORE IMPORTANT CONSTITUENTS.

Class.	Oil.	Botanical Source.	Main Constituents.
Oils containing hydrocarbons	Turpentine	Species of *Pinus*	Terpenes (chiefly *d*- and *l*-pinene). Resinous oxidation products.
	Juniper	*Juniperus communis*	Terpenes (pinene), sesquiterpenes (cadinene), terpene alcohols (juniper camphor).
	Cubebs	*Piper Cubeba*	Sesquiterpenes.
	Copaiba	Species of *Copaifera*	Sesquiterpenes.
	Cade	*Juniperus Oxycedrus*	Sesquiterpenes (cadinene, 20-30 %), phenols (5 %).
Oils containing alcohols	Rosemary	*Rosmarinus officinalis*	Alcohols (borneol, 10-16 %), esters (bornyl acetate, 2-5 %), cineole, ketones (camphor), terpenes.
	Peppermint	*Mentha piperita*	Alcohols, 50-80 % (*l*-menthol), esters (5 %), aldehydes, ketones, terpenes.
	Coriander	*Coriandrum sativum*	Alcohols (*d*-linalol, 45-70 %), terpenes (20 %).
	Lavender	*Lavandula vera*	Alcohols (linalol), esters (linalyl acetate), the proportions differing widely in English and French oils. Cineole, 20-30 %.
	Rose	*Rosa damascena*	Alcohols, 70-75 % (geraniol, citronellol), solid hydrocarbons.
	Nutmeg	*Myristica fragrans*	Alcohols (*d*-borneol, geraniol, α-terpineol), phenols (eugenol), phenolic ethers, terpenes.
	Sandal wood	*Santalum album*	Sesquiterpene alcohols (α- and β-santalols, 92-98 %).

ESSENTIAL OILS CLASSIFIED ACCORDING TO THEIR MORE IMPORTANT CONSTITUENTS.—*Cont.*

Class.	Oil.	Botanical Source.	Main Constituents.
Oils containing cineole	Cajuput	Species of *Melaleuca*	Cineole (45 % or more), hydrocarbons, alcohols, aldehydes.
	Eucalyptus	Species of *Eucalyptus*	Cineole (55 % or more), other constituents varying with the species of *Eucalyptus*.
Oils containing aldehydes	Cinnamon	*Cinnamomum zeylanicum*	Aldehydes, (cinnamic aldehyde, 55-75 %), phenols (eugenol), hydrocarbons.
	Lemon-grass	Species of *Cymbopogon*	Aldehydes, 70-85 % (citral), alcohols, esters, terpenes.
	Lemon	*Citrus Medica* var. *β-Limonum*	Aldehydes (citral, 4-5 %; citronellal), esters, hydrocarbons, 90 % (*d*-liminene).
Oils containing ketones	Dill	*Peucedanum graveolens*	Ketones (*d*-carvone, 40-60 %), terpenes.
	Caraway	*Carum Carvi*	Ketones (*d*-carvone, 45-60 %), terpenes.
	Spearmint	*Mentha viridis* and *M. crispa*	Ketones (*l*-carvone, 42-60 %), alcohols, esters, terpenes.
Oils containing phenols and phenolic ethers	Ajowan	*Carum copticum*	Phenols (thymol, 35-45 %; carvacrol), terpenes.
	Cloves	*Eugenia caryophyllata*	Phenols, 84-95 % (eugenol), alcohols, ketones, esters, sesquiterpenes.
	Aniseed	*Pimpinella Anisum* and *Illicium verum.*	Phenolic ethers (anethole, 80-90 %).
Oils containing esters	Siberian fir	*Abies sibirica*	Esters (bornyl acetate, 30-40 %), terpenes.
	Chamomile	*Anthemis nobilis*	Esters (derived from higher aliphatic alcohols and unsaturated acids), hydrocarbons.
	Wintergreen	*Gaultheria procumbens* and *Betula lenta*	Esters (methyl salicylate, 99 %).
	Mustard	*Brassica sinapioides*	Esters (allyl iso-thiocyanate, 92-99 %).

CHAPTER XIII.

RESINS AND RESINOUS SUBSTANCES.

Resins.

Resins form an ill-defined group of plant products which are produced normally during growth or secreted as a result of injury to the plant.

As a class, resins are related to one another more by their physical properties and appearance than by any similarity in chemical composition. They are usually brittle amorphous solids which fuse readily on heating, after passing through a preliminary stage of softening. They are insoluble in water, but dissolve in alcohol or other organic solvents forming solutions which, on evaporation, deposit the resin as a varnish-like film. Resins burn with a characteristic smoky flame.

Many resins are believed to be oxidation products of the terpenes. They are usually more or less complex mixtures, and their main constituents may be conveniently classified as follows :—

Resin alcohols.—Complex alcohols of high molecular weight, which are distinguished as "resinotannols" or "resinols," according as to whether they do or do not give a tannin reaction with iron salts. Resin alcohols are present in resins both in the free state and, as "resin esters," in combination with simple aromatic acids (such as benzoic, salicylic, cinnamic, and umbellic).

Resin Acids.—Substances of exceedingly complex composition which usually combine the properties of carboxylic acids and phenols. They occur in resins both in the free state and as esters. The free acids are soluble in aqueous alkalis, usually forming soap-like solutions or colloidal

suspensions. The metallic salts of resin acids are known as resinates, and some of them find extensive applications in the manufacture of cheap soaps and varnishes.

Resenes.—Complex neutral substances, practically devoid of characteristic chemical properties. They do not form salts or esters, and are insoluble in, and resist hydrolysis by, alkalis.

Colophony resin, or common " rosin," is the cheapest and by far the most important resin, and is obtained from the oleo-resin of various species of *Pinus.* The crude oleo-resin is distilled with water, when oil of turpentine passes over, leaving a residue of colophony, which is strained into barrels while still molten.

Colophony is a brittle, translucent resin, which varies in colour according to the quality from very pale amber to nearly black. It begins to soften at about 80°, and becomes completely molten at something over 100°. It is insoluble in water, but dissolves freely in most organic solvents, in fixed and volatile oils, and in solutions of caustic alkalis.

Colophony consists largely of resin acids. Crude " abietic acid " can be extracted from colophony, by means of alcohol and hydrochloric acid, in yields of 70 per cent. or more. It is a mixture of optically active acids of the molecular formula $C_{20}H_{30}O_2$. The abietic acids are monobasic, contain two double bonds,[1] and probably contain a phenanthrene nucleus.[2] The current view is that abietic acid, as such, is not present in the crude oleo-resin exuded by the plant, but is formed by isomerisation of the primary resin acids under the influence of heat or mineral acids.[3]

When colophony is distilled it undergoes complex decomposition. The product passing over between 80° and 250° is known as " rosin spirit," and consists mainly of aliphatic, aromatic, and terpene hydrocarbons. " Rosin oil," a more viscous liquid, consisting of high boiling-point hydrocarbons, together with abietic acid, and, possibly, its anhydride, distils above 300°. Rosin spirit and rosin oil are important commercial products, the oil in particular being widely employed as a lubricant.

[1] Levy and Raalf, *Ber.*, 1926, **59,** 1302.
[2] Ruzicka and Pfeiffer, *Helv. Chim. Acta,* 1925, **8,** 632.
[3] Dupont, Desalbres, and Bernette, *Bull. Soc. Chim.*, 1926 (iv.), **39,** 488.

Tests for colophony.—1. Dissolve in petroleum spirit, and shake with a 0·1 per cent. solution of cupric acetate. Note the emerald green colour slowly developed.

2. Pour about 20 drops of a 1 per cent. solution of colophony in acetic anhydride into a porcelain dish. Add 2 or 3 drops of concentrated sulphuric acid, and note the wine-red colour, slowly changing to brown.

Guaiacum resin occurs in large masses or rounded tears, usually covered with a greenish powder. The resin is brittle, and breaks with a conchoidal fracture, exposing a reddish-brown surface which turns green on exposure to air. It melts indefinitely at about 85°.

Guaiacum resin consists almost entirely of resin acids, together with small quantities of colouring matters, etc. It is remarkable in that it contains a substance which yields a deep blue oxidation product (" guaiacum blue ").

Test for guaiacum resin.—Guaiacum resin is easily recognised by the blue coloration it yields with oxidising agents. Dissolve a little of the resin in alcohol and add a drop or two of ferric chloride solution, when an intense blue coloration is produced.

Gum-resins and oleo-resins.

Gum-resins, such as gamboge, are simply mixtures consisting chiefly of resin and gum. The gum is usually a glucosidal substance similar in composition to gum acacia.

Oleo-resins are more or less homogeneous mixtures of resins and volatile oils. The term " oleo-gum-resin " is sometimes applied to substances, such as myrrh, which consist of mixtures of resins, gums, and volatile oils.

There is no sharp line of demarcation between these various types of resinous substances, and classification is sometimes difficult; thus guaiacum resin, which is not usually regarded as a gum-resin, may contain as much as 10 per cent. of gum, whilst small proportions of volatile oil are present in many resins, such as mastich and sandarac.

Myrrh is an important oleo-gum-resin. It occurs in irregular lumps of agglutinated tears, which are dull reddish-brown externally. The freshly fractured surface is brighter in colour than that which has been exposed to air, and frequently shows whitish markings. Myrrh has a pleasant, fragrant odour, and a bitter taste.

True myrrh is probably obtained from *Commiphora Myrrha*, but myrrh, as imported from the East, frequently

Resin.	Botanical or Zoological Source.	Constituents.		
		Resin Alcohols.	Resin Acids.	Resenes.
Colophony	Species of *Pinus*	—	82-94 %, chiefly abietic acid, $C_{20}H_{30}O_2$.	5 %.
Burgundy pitch	*Picea excelsa*	—	α- and β-picea-pimarolic acids, picea-pimarinic acid, picea-pimaric acid	Juroresene.
Guaiacum	*Guaiacum officinale* and *G. sanctum*	—	α- and β-guaiaconic acids (70 %), guaiaretic acid (11 %), guaiacic acid	——
Mastich	*Pistacia Lentiscus*	—	α- and β-masticonic acids (38 %), α- and β-masticic acids (4 %), masticolic acid (0·5 %)	α- and β-masticoresenes (50 %).
Sandarac	*Callitris quadrivalvis*	—	Sandaracopimaric acid (85 %), sandaracinic acid, sandaracinolic acid	Sandaracoresene.
Dragon's blood	Species of *Dæmonorops*	Dracoresinotannol as its benzoic and benzoyl acetic esters (57 %)	——	Dracoresene (14 %), dracoalban (2·5 %).
Shellac	*Coccus lacca*	—	Aleuritic acid, $C_{15}H_{28}(OH)_3 . COOH$, and shelloic acid, probably combined together.	——

contains other oleo-gum-resins derived from species of *Commiphora* and *Balsamodendron*. These are separated by hand, and the picked myrrh is sold as "gum myrrh elect." A common adulterant of myrrh is bissabol or perfumed bdellium, and this, as well as several other bdelliums, fails to respond to the following test, which seems to be characteristic of the genuine drug :—

Test for myrrh.—Shake a little myrrh with ether, decant the liquid on to a watch-glass, and allow to evaporate. Add to the residual film a few drops of 50 per cent. nitric acid, when a violet colour is produced. A similar coloration is formed by exposure of the film to the vapour of concentrated nitric acid or of bromine.

Myrrh contains about 20-40 per cent. of resin, 50-60 per cent. of gum, and 2·5-8 per cent. of volatile oil. The resin consists largely of three ether-soluble resin acids, which have been termed α-, β-, and γ- commiphoric acids ; [1] it also contains resin acids insoluble in ether, resenes, and complex phenolic compounds. The volatile oil contains terpenes, sesquiterpenes, aldehydes, and phenols. The gum is similar to acacia.

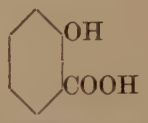
The percentage of alcohol-soluble substances in myrrh is very variable, and on this account tinctures of myrrh contain widely varying percentages of dissolved matter.

Ammoniacum, galbanum, and **asafetida** are oleo-gum-resins which are all obtained from plants of the natural order *Umbelliferæ*. They are met with in the form of tears, or in agglutinated masses containing varying amounts of earthy matter and vegetable débris. The unpleasant odour of asafetida is due to its volatile oil, which contains various malodorous sulphur compounds.

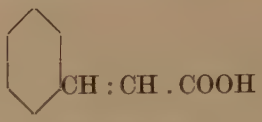
Ammoniacum, galbanum, and asafetida all contain some 20 per cent. of gum, the remainder consisting largely of resins, composed of resinotannols combined with salicylic acid, umbelliferone, or ferulic acid. The composition of the individual resins is summarised in the table on page 128, and it is unnecessary to discuss them further. The following formulæ show the relationship of salicylic acid, umbelliferone, and ferulic acid to each other, and to other simple and important aromatic compounds which occur in drugs :—

[1] Friedrichs, *Arch. Pharm.*, 1907, **245**, 427.

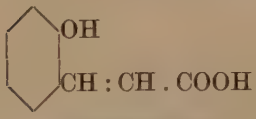
Benzoic acid.



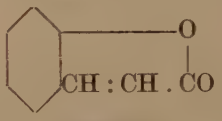
Salicylic acid
(hydroxy-benzoic acid)



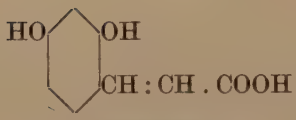
Cinnamic acid



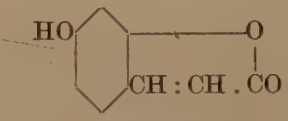
Coumarinic acid
(hydroxy-cinnamic acid)



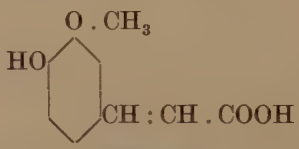
Coumarin
(lactone of coumarinic acid)



Umbellic acid
(dihydroxy-cinnamic acid)

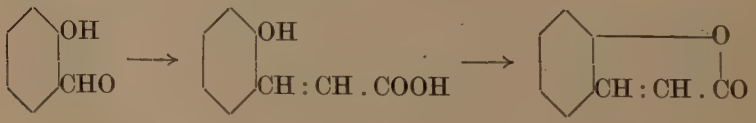


Umbelliferone
(lactone of umbellic acid)



Ferulic acid
(hydroxy-methoxy-cinnamic acid)

Benzoic and cinnamic acids are important constituents of balsams (*q.v.*). Coumarin is mentioned here on account of its close relationship to cinnamic acid and to umbelliferone ; it is a pleasant smelling, crystalline compound, and is the odoriferous constituent of tonco beans (species of *Dipteryx*), in which it occurs to the extent of about 3 per cent. Coumarin is used in perfumery, and considerable quantities are prepared synthetically by boiling together salicylaldehyde, acetic anhydride, and anhydrous sodium acetate (Perkin's reaction) :—



Distinction between ammoniacum, galbanum, and asafetida.—1. *Test for salicylic acid.*—Add a drop of ferric chloride solution to a clear ethereal extract of the drug. A faint violet colour is produced with ammoniacum, but not with galbanum or asafetida.

2. *Test for free umbelliferone.*—Boil a small quantity of the drug with 90 per cent. alcohol; cool, and decant the solution through a filter into alcohol containing ammonia. A blue fluorescence is given with galbanum, but not with ammoniacum or asafetida.

3. *Test for combined umbelliferone.*—Boil a small quantity of the drug with concentrated hydrochloric acid for a few minutes; dilute the liquid with an equal volume of water, and filter as in the previous test into alcoholic ammonia. A blue fluorescence is given by asafetida and galbanum, but not by Persian ammoniacum.

4. *Distinction between Persian and African ammoniacums.*—Grind up with water, and add sodium hypochlorite solution. Persian ammoniacum gives an orange-red colour, but African does not. Also note that African ammoniacum gives a positive result in the test for combined umbelliferone. African ammoniacum is not used medicinally, and is rarely met with in commerce.

Balsams.

Oleo-resins are sometimes spoken of as balsams (e.g. Canada balsam), but this term is more properly restricted to resinous substances which contain large proportions of free or combined benzoic or cinnamic acids.

Balsam of Tolu (*Myroxylon Toluifera*) is a soft resinous substance which hardens on keeping. It contains from 70 to 80 per cent. of resin, consisting mainly of toluresinotannol combined with benzoic and cinnamic acids. The balsam also contains free benzoic and cinnamic acids, and about 7·5 per cent. of oil (chiefly benzyl benzoate). The total aromatic acid content is approximately as follows: Benzoic acid, 15 per cent. (8 per cent. free, 7 per cent. combined); cinnamic acid, 20-23 per cent. (12-15 per cent. free, 8 per cent. combined).

Balsam of Peru (*Myroxylon Pereiræ*) is a dark-coloured viscous liquid containing about 28 per cent. of resin (peruresinotannol combined with cinnamic and a little benzoic acid). The liquid portion of the balsam (about 50-66 per cent.) consists of a mixture of benzyl benzoate and benzyl cinnamate, the mixture being sometimes known as "cinnamein."

Crude storax (*Liquidambar orientalis*) is a balsam which contains about 20-30 per cent. of substances insoluble in alcohol, much of which consists of vegetable débris. For

Drug.	Botanical Source.	Resin.	Gum.	Volatile Oil.	Constituents of the Resin.
Scammony	*Convolvulus Scammonia*	70-90 %	10-15 %	—	Resin identical with that obtained from the dry root (see Gluco-resins).
Gamboge	*Garcinia Hanburii*	70-80 %	15-20 %	—	"Garcinolic acids," resin esters, and a resene.
Myrrh	*Commiphora Myrrha*	25-40 %	50-60 %	2·5-8·0 %	α-, β-, and γ-commiphoric acids, other resin acids, resenes, complex phenolic compounds.
Olibanum	*Boswellia Carterii* and other species	60-70 %	20-30 %	5-10 %	Boswellic acid (free and combined), olibanoresene.
Ammoniacum	*Dorema Ammoniacum* and other species	65-70 %	20 %	0·5 %	Ammoresinotannol combined with salicylic acid, free salicylic acid (traces), and a resene.
Galbanum	*Ferula galbaniflua* and other species	60-65 %	20 %	5-15 %	Galbaresinotannol combined with umbelliferone, free umbelliferone (traces).
Asafetida	*Ferula fœtida, F. rubricaulis,* and other species	40-65 %	25 %	4-20 %	Asaresinotannol combined with ferulic acid. On boiling with acids, yields free umbelliferone.
Canada turpentine	*Abies balsamea* and *A. canadensis*	70-80 %	—	18-24 %	α- and β-Canadinolic acids (48-60 %), canadinic acid (13-20 %), canadolic acid (0·5-3·0 %), canadoresene (1-20 %).
Copaiba (Maracaibo)	Species of *Copaifera*	40-60 %	—	40-50 %	β-Meta-copaivic acid, $C_{10}H_{16}O_2$, illuric acid, $C_{20}H_{28}O_3$, copaivic acid, copaiboresenes.

pharmaceutical purposes the alcohol-soluble portion is employed under the name of "purified storax."

Purified storax is a reddish-brown, semi-solid balsam which is remarkable for its high cinnamic acid content. The resin, which forms about 36 per cent. of the drug, consists of storesinol, partly free and partly combined with cinnamic acid. The liquid portion consists mainly of cinnamic esters. The cinnamic acid content varies from 20 to as much as 47 per cent., of which about 20 per cent. or more may be free.

Sumatra benzoin (*Styrax Benzoin*) occurs in brittle, brown, resinous masses, in which white tears are embedded. It contains about 70-95 per cent. of resin (a complex alcohol, lubanol, combined with cinnamic and a little benzoic acid). The aromatic acid content of the drug is approximately as follows : Cinnamic acid, 17 per cent. (10 per cent. free, 7 per cent. combined) ; benzoic acid, 8·5 per cent. (6 per cent. free, 2·5 per cent. combined).

Other commercial varieties of benzoin, such as the Palembang and Siamese, contain large proportions of benzoic acid and very little cinnamic.

Test for Sumatra benzoin.—Warm gently with potassium permanganate solution, when an odour of benzaldehyde is evolved, owing to oxidation of the cinnamic acid :—

$$C_6H_5 . CH : CH . COOH \rightarrow C_6H_5 . CHO.$$

Siamese and Palembang benzoins do not contain sufficient cinnamic acid to respond to this test.

Gluco-resins.

Substances known as gluco-resins occur in such drugs as jalap, scammony, and turpeth roots, from which they may be obtained by extracting with alcohol and precipitating the resin by pouring the alcoholic solution into water. As thus obtained, the gluco-resins are complex mixtures. On hydrolysis, they yield sugars and complex resin acids which appear to be combined in the drug in the form of glucosides.

Orizaba jalap root (*Ipomœia orizabensis*) yields 12-18 per cent. of resin, about 65 per cent. of which is ether-soluble. The resin is a complex mixture, and from the products of hydrolysis of the ether-soluble portion have been isolated jalapinolic acid and its methyl ester, and sugars (glucose and a methyl pentose). The resin thus appears to consist largely

of the glucosides and methyl pentosides of jalapinolic acid and methyl jalapinolate.

Scammony root (*Convolvulus Scammonia*) yields 3-13 per cent. of resin, which is almost entirely soluble in ether. In chemical composition and therapeutic action it is very similar to the ether-soluble portion of the resin of orizaba jalap root, and for this reason the British Pharmacopœia permits the use of resin from either orizaba jalap or scammony under the name of scammony resin, provided that not less than 75 per cent. of it is soluble in ether.

The products of hydrolysis show that scammony resin consists mainly of the glucosides and methyl pentosides of jalapinolic acid and its methyl ester. The methyl pentose has been identified as rhamnose, and appears to be different from the methyl pentose isolated from the products of hydrolysis of orizaba jalap resin.

Jalap root (*Ipomœia Purga*) yields 2-22 per cent. of resin, only 10-15 per cent. of which is ether-soluble. The ether-soluble portion closely resembles the ether-soluble portions of scammony and orizaba jalap resins, and is therefore sometimes called "scammonin." The portion insoluble in ether is termed "jalapin," and is a complex mixture, which appears to consist partly of the glucosides of convolvulinolic and ipurolic acids.

Kaladana resin (*Ipomœia hederacea*) was formerly believed to be identical with the ether-insoluble resin of jalap, but it has been shown to consist of a purgative non-glucosidal resin mixed with large proportions of glucosidal matter.[1]

Turpeth root (*Ipomœia Turpethum*) yields 5-10 per cent. of resin, which is partly soluble in ether. The resin has not been thoroughly investigated, but the ether-soluble portion seems to consist of a rhamnoside (α-turpethein) and a glucoside (β-turpethein). The portion insoluble in ether is known as "turpethin."

[1] Kassner, *Pharm. J.*, 1924, **112**, 357.

CHAPTER XIV.

ANIMAL PRODUCTS.

Some few drugs of animal origin (such as animal fats, fish oils, waxes, and cochineal) have already been dealt with in chapters in which they naturally fall. Other types of animal products used in medicine will now be described.

Drugs containing digestive enzymes.

Pepsin.—The glands which line the stomachs of higher animals secrete a substance known as pepsin. For medicinal purposes pepsin is obtained by macerating the minced mucous membrane of the stomach of the pig, sheep, or calf with very dilute hydrochloric acid, filtering, and precipitating with ammonium sulphate or sodium chloride. The precipitated pepsin is separated, dissolved in water, and freed from inorganic salts by dialysis. It is recovered from the dialysed liquid by precipitation with alcohol or by evaporation to a syrup and subsequent "scaling," with or without the addition of small quantities of dextrin.

Commercial pepsin prepared by the above methods is met with as a nearly white amorphous powder or straw-yellow scales, and forms with water a clear colloidal suspension. It consists mainly of true pepsin, an enzyme which owes its medicinal value to the fact that it is capable of bringing about the hydrolysis of proteins, with formation of soluble proteoses, peptones, and amino-acids. As an example of its action, it may be mentioned that the British Pharmacopœia requires that pepsin should dissolve 2500 times its weight of coagulated egg albumen in six hours.

Pepsin acts only in a faintly acid medium, such as is normally produced in the stomach by acid-secreting glands. Its activity is destroyed by heating to about 70°.

Pancreatin.—The pancreas of animals contains enzymes capable of causing the hydrolysis of proteins, fats, and starches, and the curdling of milk. The more important of these enzymes are trypsin, lipase, and amylase.

Trypsin brings about the hydrolysis of proteins, with formation of simple soluble polypeptides and amino-acids, through the intermediate formation of proteoses and peptones. Trypsin differs from pepsin in that it acts best in a slightly alkaline medium (for example, in the presence of bile in the duodenum).

Lipase hydrolyses fats to fatty acids and glycerin.

Amylase is a diastatic enzyme which hydrolyses starch with formation of maltose.

The pancreatin of commerce is obtained by extracting the minced pancreas of the hog with water or dilute hydrochloric acid, precipitating with alcohol, separating the precipitate, and drying below 40°. Pancreatin contains the typical enzymes of the pancreas, and is met with as a white or yellowish amorphous powder, or in transparent, yellowish scales.

Pancreatic solutions are prepared by macerating finely divided pancreas with a mixture of water, alcohol, and glycerin.

Test for trypsin in pancreatic solution.—The following experiment illustrates the protein-splitting action of trypsin :—

To about 80 c.cs. of milk, add a solution of 0·2 gram of sodium bicarbonate in 20 c.cs. of water, together with about 6 c.cs. of pancreatic solution. Keep the mixture at about 45° for an hour. Transfer 5 c.cs. of the liquid to a small stoppered measuring cylinder, add an equal volume of ether (to dissolve the liberated fat-acids) and a few drops of concentrated nitric acid. Shake gently and allow to separate, when it will be noticed that no curdy precipitate is present in the aqueous layer, owing to the fact that the protein matter of the milk has been hydrolysed with formation of water-soluble substances. Compare the result with that of a blank experiment in which no pancreatic solution is used.

Ox bile.

Ox bile, or ox gall, is secreted by the liver of the ox. It is a brownish, or dark green, somewhat viscous, faintly alkaline liquid, with a characteristic unpleasant odour and a bitter taste.

The main constituents of bile are :—

The sodium salts of glycocholic and taurocholic acids (the "bile acids").
Bilirubin and biliverdin (the "bile pigments").
Small quantities of nucleo-proteins, lecithin, etc.
Cholesterol.

Glycocholic and **taurocholic** acids are complex substances which yield, on hydrolysis, cholalic or cholic acid,

$$C_{23}H_{36}(OH)_3 . COOH$$

and a simple amino-acid :—

$$C_{23}H_{36}(OH)_3 . CO . NH . CH_2 . COOH + H_2O$$

Glycocholic acid

$$= C_{23}H_{36}(OH)_3 . COOH + NH_2 . CH_2 . COOH$$

Cholalic acid — Glycine

$$C_{23}H_{36}(OH)_3 . CO . NH . CH_2 . CH_2 . SO_3H + H_2O$$

Taurocholic acid

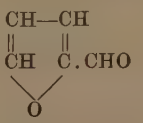
$$= C_{23}H_{36}(OH)_3 . COOH + NH_2 . CH_2 . CH_2 . SO_3H.$$

Cholalic acid — Taurine

Purified ox bile is prepared by evaporating ox bile to small bulk, adding alcohol to precipitate nucleo-proteins, etc., decanting or filtering, and concentrating to a soft extract. It is a thick, yellowish-brown or yellowish-green extract.

Test for bile acids (Pettenkoffer's reaction).—Add a few drops of freshly prepared cane sugar solution to a few centigrams of purified ox bile in 10 c.cs. of water. Slowly run in about 5 c.cs. of concentrated sulphuric acid, when the mixture becomes red, the colour changing, on standing, to purple and then to violet.

In this test, the sulphuric acid acts on the sugar, forming furfuraldehyde,



Furfuraldehyde

and this gives a purple colour with cholalic acid, produced by hydrolysis of the bile acids.

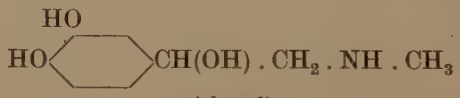
Liver extract.

Until the recent discovery by Minot and Murphy of the value of raw or lightly-cooked liver in the treatment of pernicious anæmia, this disease was regarded as practically incurable. In order to avoid the unpleasantness of taking large quantities of liver daily in an unpalatable form, extracts are now being manufactured of which a few grams will produce the same effect as a pound or so of liver. The efficacy of liver extracts have been investigated and approved by the Medical Research Council in a preliminary report.[1]

Hormones.

The bodies of higher animals contain minute ductless glands, sometimes known as endocrine organs, which pass their products directly into the blood stream or lymph channels. These products are, therefore, sometimes known as increta, in order to distinguish them from the excreta of such glands as those producing saliva, sweat, or urine. Endocrine glands produce definite chemical substances called "hormones" (Greek, "hormao"—to stir up or excite) which are able, when carried to other parts of the body, to produce definite responses in organs far removed from those in which they were produced. Thus, for example, a hormone, secretin, produced in the duodenum, causes the secretion of pancreatic juice by the pancreas.

Adrenalin.—Suprarenal glands of animals owe their hæmostatic properties to the presence of about 0·1 per cent. of a hormone, adrenalin :—



Adrenalin

Adrenalin may be extracted from the glands by means of dilute acid, and obtained, after concentration of the extract, by precipitation with ammonia.

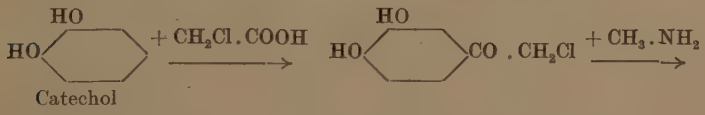
Adrenalin is a colourless crystalline compound, sparingly soluble in water. An inspection of its formula will show that the molecule contains an asymmetric carbon atom, and the

[1] See *Lancet*, March 10th, 1928, p. 514; *B.M.J.*, March 10th, 1928, p. 398.

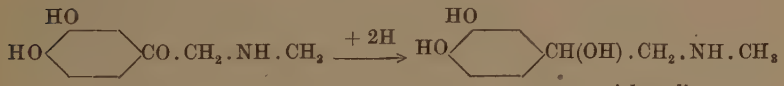
naturally occurring substance is lævorotatory. Chemically, adrenalin has the usual properties of a secondary base, and dissolves in dilute acids to form salts. It is also a phenol, and, consequently, dissolves freely in solutions of caustic alkalis ; like other dihydric phenols, it readily undergoes oxidation.

A solution of adrenalin in dilute hydrochloric acid gives with ferric chloride a green colour, changing on cautious addition of sodium hydroxide first to violet and finally to red. Adrenalin can be detected in suprarenal gland by treating an aqueous sulphuric acid extract with sodium acetate and mercuric chloride, when a red coloration is produced. This test can be applied to the quantitative colorimetric estimation of adrenalin in suprarenal powders.[1]

Adrenalin was synthesised over twenty years ago. It can be prepared from catechol by condensing it with chloracetic acid, when a compound is produced which, by interaction with methylamine and subsequent reduction with aluminium amalgam, yields inactive adrenalin :—



Catechol



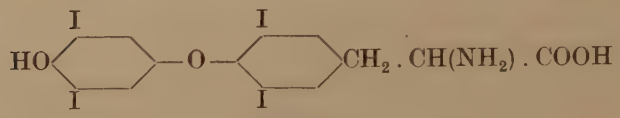
Adrenalin

The product can be resolved into its optically active components by means of its *d*-tartrate.

Thyroxin.—Thyroid glands are obtained, for medicinal purposes, from the sheep. The active principle is the hormone thyroxin, $C_{15}H_{11}O_4NI_4$, which has been isolated from the glands in yields as high as 0·027 per cent.[2]

Thyroxin, which produces physiological effects similar to those characteristic of the glands, has been synthesised by Harington and Barger,[3] and has the following formula :—

[1] Bailly, *J. Pharm. Chim.*, 1924 (vii.), **30,** 404.
[2] Harington, *Biochem. J.*, 1926, **20,** 293.
[3] *J. Soc. Chem. Ind.*, 1926, **45,** 931.



Thyroxin

Formerly, thyroxin was believed to be $C_{11}H_{10}O_3NI_3$, and an erroneous structural formula was advanced by Kendall on this supposition.

Thyroxin is a colourless, crystalline compound which dissolves in alkalis with formation of metallic salts. Commercial " thyroxin " is the crude sodium salt, and has about 5000 times the activity of the fresh gland.

Insulin.—Fresh pancreas contains small amounts of a hormone, insulin, which is produced by minute ductless glands, dispersed throughout the pancreas, and known as the " Islets of Langerhans."

Insulin is a commercial product of considerable importance, owing to its value in the treatment of diabetes. The crude hormone was first obtained and investigated by Banting and Best and their collaborators,[1] and although the active constituent is not yet obtainable as a pure chemical compound, recent methods of purification have led to the production of samples of insulin of greatly increased physiological activity.[2]

Little is known of the chemistry of insulin, but it appears to be a complex substance of the nature of a proteose,[3] and is destroyed by digestion with trypsin. Consequently, in the extraction of insulin from pancreas, the hydrolytic action of the trypsin must be prevented, and this is usually done by storing the fresh glands at a temperature below 0°, and employing alcohol as the extracting medium. Crude insulin may be purified by several methods, one of the most important of which involves the precipitation of the hormone as its picrate and the conversion of this into " insulin hydrochloride " by the action of hydrochloric acid in alcoholic solution. Details of a large-scale process for the manu-

[1] *J. Laborat. Clin. Med.*, 1922, **7,** 251 ; *Amer. Chem. Abs.*, 1922, **16,** 1980 and 3115.

[2] Abel (*Proc. Nat. Acad. Sci.*, 1926, **12,** 132) claims to have isolated insulin as a crystalline compound of definite melting-point.

[3] Funk (*Science*, 1926, **63,** 401) suggests that insulin is a complex polypeptide of the formula $C_{69}H_{102}O_{22}N_{18}S$ or $C_{74}H_{114}O_{24}N_{20}S$.

facture of insulin are given by Carr [1] and reference may be made to the original paper.

Insulin is commonly standardised by measurements of its effect on the sugar content of the blood of rabbits. A sample of insulin hydrochloride prepared by the Medical Research Council of Great Britain was accepted as a standard for purposes of biological assay by the International Conference on Biological Standards (Geneva, Sept., 1925).

Gelatin.

Gelatin is prepared by boiling bone cartilage with water, straining, and evaporating. During the boiling, gelatin is produced from a substance known as *collagen*, which forms part of the cartilage.

Gelatin occurs in the form of semi-transparent, colourless, or pale yellow sheets, or in shreds. On treatment with cold water it swells, and dissolves, on heating, to form a liquid which, if not too dilute, sets to a jelly on cooling.

Gelatin is a substance of the nature of a protein, and is readily hydrolysed with formation of simple amino-acids. In this connection it may be noted that, if gelatin is boiled for any length of time with water, it may become hydrolysed, and will then fail to set to a jelly on cooling.

Gelatin capsules which are required to dissolve only in the intestine may be dipped in a solution of formaldehyde and dried, the gelatin being in this way rendered hard and insoluble.

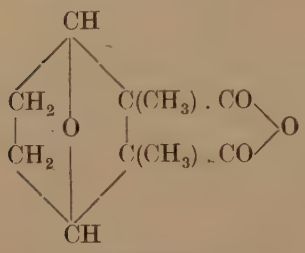
Cantharides.

Various insects of the order *Coleoptera* possess vesicant properties which are due to a colourless, crystalline compound known as **cantharidin,** which is present to the extent of about 0·5-0·8 per cent. in Spanish flies (*Cantharis vesicatoria*), and 1·0 per cent. or more in Chinese blistering beetles (*Mylabris sidæ* and *M. cichorii*).

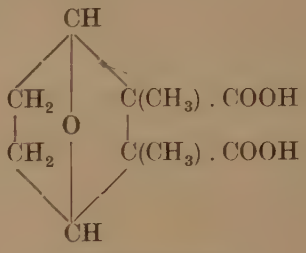
Cantharidin was obtained in quantity from the insects as long ago as 1835, but its constitution was not thoroughly investigated until Gadamer commenced the publication of his researches in 1913. Cantharidin has the properties of

[1] *J. Soc. Chem. Ind.*, 1924, **43,** 228 T.; see also *Pharm. J.*, 1927, **118,** 244.

the inner anhydride of a dibasic acid, and of the various formulæ proposed by Gadamer,[1] preference has been given to the following :—[2]



Cantharidin
(anhydride of cantharidic acid)



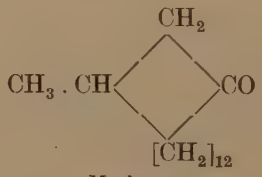
Cantharidic acid

Cantharidin reacts with caustic alkalis to form salts of the corresponding dibasic acid (cantharidic acid), and there is no doubt that the beetles contain soluble salts of cantharidic acid in addition to cantharidin.

Musk.

Musk, a dried secretion obtained from the musk deer (*Moschus moschiferus*), yields, on steam distillation, about 1·4 per cent. of a dark brown oil.

Muskone, or muscone, $C_{16}H_{30}O$, the main odoriferous constituent of the oil, was isolated by Walbaum [3] as a colourless liquid. It has recently been shown that muskone is a cyclic ketone containing a closed chain of no less than fifteen carbon atoms,[4] and it probably has the following structure :—



Muskone

[1] *Arch. Pharm.*, 1914, **252,** 609.

[2] Rudolph, *Arch. Pharm.*, 1916, **254,** 423; Gadamer, *Arch. Pharm.*, 1917, **255,** 277, 290, 315; 1920, **258,** 171.

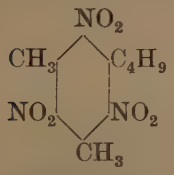
[3] *J. pr. Chem.*, 1906 (ii.), **73,** 488.

[4] Ruzicka, *Helv. Chim. Acta*, 1926, **9,** 715.

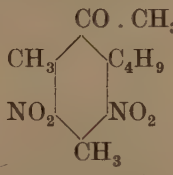
Civetone, the odoriferous product of the civet cat, is an unsaturated cyclic ketone containing a closed chain of seventeen carbon atoms.

The recent work on the structure of muskone and civetone is of particular interest, in that these compounds provide the only known examples of the occurrence of large carbon rings in plant or animal products.

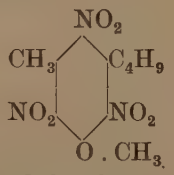
" Artificial musks " are synthetic products which reproduce, to some extent, the odour of natural musk. The best-known substance of this class is " musk-xylene " (a trinitro tertiary butyl xylene), but other similar nitro compounds with musk-like odours are widely used in perfumery, as, for example, " ketone-musk " and " musk-ambrette " :—



Musk-xylene

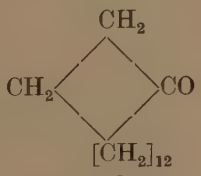


Ketone-musk



Musk-ambrette

It seems probable that such artificial musks will eventually be superseded by synthetic compounds closely related in structure to muskone itself. Already, cyclo-pentadecanone is being manufactured, as a substitute for musk, under the trade name " exaltone " :—



Cyclo-pentadecanone

CHAPTER XV.

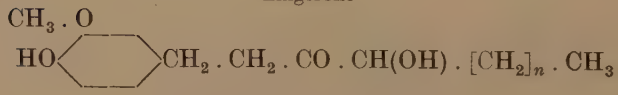
MISCELLANEOUS DRUGS.

Pungent principles.

Ginger rhizome (*Zingiber officinale*) contains about 2 per cent. of volatile oil, but the pungent properties are due to the presence of a substance which has long been known as "gingerol," and which has the general properties of an oleo-resin.

When gingerol is boiled with baryta water or subjected to the action of a current of steam, it becomes hydrolysed with formation of a mixture of volatile aliphatic aldehydes (mainly normal heptaldehyde) together with a pungent, crystalline, phenolic ketone which has been termed *zingerone*.[1] The oleo-resin "gingerol" consists essentially, therefore, of a mixture of homologous phenolic compounds derived from zingerone and various aliphatic aldehydes. The relationship of the constituents of the oleo-resin to the simple ketone, zingerone, may be represented thus :—

Zingerone



Gingerol (where $n = 3$, 4, and 5)

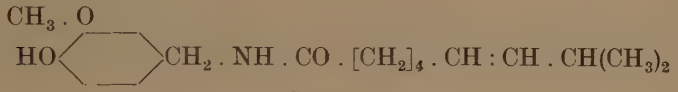
The formula of zingerone has been placed beyond doubt by its synthetic preparation by two different methods.[2]

[1] Nomura, *Trans. Chem. Soc.*, 1917, **111**, 769; Lapworth, Pearson, and Royle, *Trans. Chem. Soc.*, 1917, **111**, 777.

[2] Nomura, *loc. cit.*; Lapworth and Wykes, *Trans. Chem. Soc.*, 1917, **111**, 790.

Grains of paradise (*Amomum Melegueta*) contain an oleoresin, paradol, which appears to be similar in composition to gingerol.[1] Paradol differs from gingerol in that its pungency is not appreciably diminished by boiling with dilute aqueous potassium hydroxide.

Capsicum fruit (*Capsicum minimum*) contains, as its pungent principle, about 0·02 per cent. of a crystalline compound, *capsaicin*, which was first isolated over 50 years ago by Thresh. Capsaicin has been examined by several investigators, and a recent synthesis of its dihydro-derivative [2] proves that capsaicin itself is an unsaturated amide of the following structure :—



Capsaicin

It will be seen that the pungent constituents of capsicum and ginger are guaiacol derivatives, and are closely related to vanillin (p. 115). It is interesting to note that dihydrocapsaicin is quite as pungent as capsaicin itself, and the former belief [3] that the pungency of capsaicin was dependent on the presence of a double bond is therefore erroneous.

Bitter principles.

Many drugs owe their action to non-glucosidal "bitter principles." These substances are usually exceedingly complex, and so little is known of their chemical nature that it is impracticable to do more than give a list of the more important of them (see next page).

Tars.

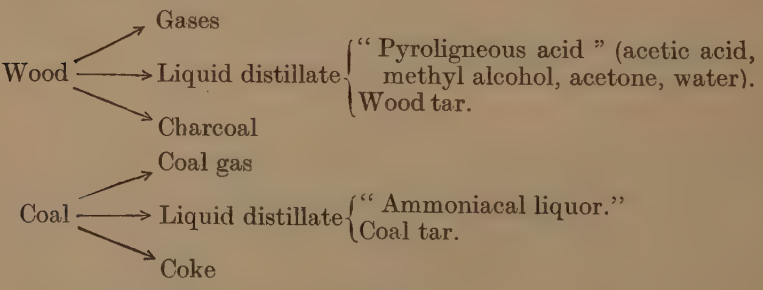
Tars are obtained by the destructive distillation of wood or coal. The process consists essentially in heating the material to a high temperature in closed retorts, when gases and vapours are evolved, leaving eventually a residue of carbon. The vapours are condensed, and the liquid separates,

[1] Nelson, *J. Amer. Chem. Soc.*, 1917, **39**, 1466.
[2] Nelson and Dawson, *J. Amer. Chem. Soc.*, 1923, **45**, 2179.
[3] Ott and Zimmermann, *Annalen*, 1921, **425**, 314.

DRUGS CONTAINING NON-GLUCOSIDAL BITTER PRINCIPLES.

Drug.	Botanical Source.	Bitter Principles.
Arnica flowers and rhizome	*Arnica montana*	Arnicin.
Calendula flowers	*Calendula officinalis*	——
Calumba root	*Jateorhiza Columba*	Columbin (a lactone) and chasmantherin.
Canella bark	*Canella alba*	——
Cascarilla bark	*Croton Eluteria*	Cascarillin.
Chiretta herb	*Swertia Chirata*	Chiratin and its products of hydrolysis (chiratogenin and ophelic acid).
Cimicifuga rhizome	*Cimicifuga racemosa*	Racemosin.
Cocculus indicus fruits	*Anamirta paniculata*	Picrotoxin.
Dandelion root	*Taraxacum officinale*	Taraxacin.
Elaterium	*Ecballium Elaterium*	β-Elaterin (purgative) and α-elaterin (inactive).
Euonymus bark	*Euonymus atropurpureus*	Euonymol (a crystalline bitter alcohol).
Hops and lupulin	*Humulus Lupulus*	Humulol (crystalline) and other bitter substances.
Quassia wood	*Picræna excelsa*	Quassin (a mixture of crystalline α- and β-picrasmins).
Serpentary rhizome	*Aristolochia Serpentaria* and *A. reticulata*	A bitter principle (probably an alkaloid).

on standing, into aqueous and tarry layers. The aqueous distillate obtained from coal contains considerable quantities of ammonia, but that from wood is acid, owing to the presence of some 10 per cent. of acetic acid. The decomposition products of wood and coal may be summarised as follows :—



Wood tar, as used for medicinal purposes, is the substance known commercially as Stockholm tar, and is obtained from various species of *Pinus*. The main constituents of wood tar

are phenols (phenol, cresols, guaiacol, creosol, catechol) and aromatic hydrocarbons (benzene, toluene, xylenes).

Creosote is an oily liquid prepared, for pharmaceutical purposes, by fractional distillation of beechwood tar. It consists principally of a mixture of guaiacol, creosol, and other phenols.

Coal tar is a very complex mixture, containing aromatic hydrocarbons (benzene, toluene, naphthalene, anthracene), phenols (phenol, cresols), and basic substances (ammonia, pyridine, etc.). Prepared coal tar, as used in pharmacy, is made by heating coal tar in an open dish at 50° for an hour, when ammonia and part of the volatile hydrocarbons are driven off.

Distinction between wood and coal tars.—Wood tar always contains traces of acetic acid, whereas coal tar contains ammonia and alkaline organic bases. Shake the tars with water and test the aqueous extracts with litmus.

Indian hemp.

Indian hemp consists of the dried flowering and fruiting tops of the pistillate plant *Cannabis sativa*, which, when grown in tropical countries, produces an oleo-resinous secretion with a well-marked physiological action. Preparations of the plant, such as "bhang" or "hashish," are largely consumed in India, and the separated oleo-resin, known as "charas," is used for smoking.

By extracting "charas" with ether and fractionally distilling the extract under diminished pressure, a highly toxic red oil is obtained, from which a toxic compound, *cannabinol*, $C_{21}H_{30}O_2$, has been isolated.[1]

Indian hemp and its preparations deteriorate rapidly on exposure to air, presumably owing to oxidation of the active constituents. The comparative physiological activities of different preparations of Indian hemp are determined by a comparison of the degree of inco-ordination which they produce when administered to animals.

Podophyllum resin.

Podophyllum resin is obtained from the rhizome of *Podophyllum peltatum* by extracting with alcohol and precipitating

[1] Czerkis, *Annalen*, 1907, **351**, 467. Compare Wood, Spivey, and Easterfield, *Trans. Chem. Soc.*, 1899, **75**, 20.

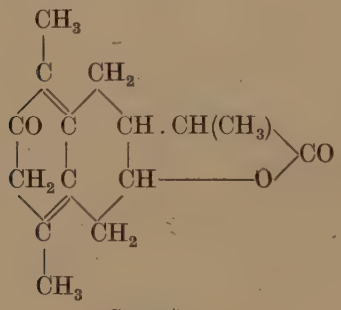
the extract with acidified water. The rhizomes yield about 3 to 10 per cent. of resin (podophyllin), of which about one-fifth consists of a crystalline, neutral, purgative substance, *podophyllotoxin*, $C_{15}H_{14}O_6$. Indian podophyllum rhizome (*P. Emodi*) yields about 10 to 12 per cent. of resin, of which nearly one-third consists of podophyllotoxin.

Wormseed.

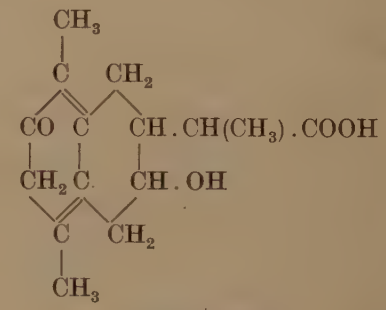
Wormseed (*Artemisia maritima*, var. *α-Stechmanniana*) contains two closely related crystalline compounds, santonin and artemisin.

Santonin, $C_{15}H_{18}O_3$, occurs in the unexpanded flower heads to the extent of 2-3 per cent., and is the main anthelmintic constituent.

Santonin is sparingly soluble in water, but dissolves in alkalis to form salts of *santoninic acid*, of which it is the lactone. Prolonged boiling with alkalis converts santoninic acid into salts of the isomeric *santonic acid*. The mutual relationship of santonin and santoninic acid is shown by the following formulæ :—



Santonin



Santoninic acid

Santonin is extracted from wormseed on the commercial scale by means of milk of lime, the lactone being thus converted into the soluble calcium salt of santoninic acid. The liquid is filtered, and treated with carbon dioxide in order to precipitate the excess of calcium as the carbonate, which is separated. Sodium carbonate is added, and the precipitated calcium carbonate filtered off, the solution of sodium santoninate being then treated with dilute sulphuric acid, when impure santonin separates. The product is purified by

decolorisation with charcoal and recrystallisation from alcohol.

Artemisin, $C_{15}H_{18}O_4$, is a hydroxy derivative of santonin, and is the lactone corresponding to *artemisinic acid*.

Liquorice root.

Liquorice root (*Glycyrrhiza glabra*, and other species) contains, in addition to sugars, starch, resin, etc., about 5 to 8 per cent. of glycyrrhizin, a soluble crystalline substance with an intensely sweet taste which persists at great dilution.

Glycyrrhizin has been investigated by Tschirch and his collaborators,[1] and was found to consist of the potassium and calcium salts of *glycyrrhizic acid*, $C_{44}H_{64}O_{19}$. On hydrolysis with boiling dilute sulphuric acid, glycyrrhizic acid yielded *glycyrrhetic acid*, $C_{32}H_{48}O_7$, and *glycuronic acid*,

$$COOH . CH(OH) . CH(OH) . CH(OH) . CH(OH) . CHO,$$

an oxidation product of glucose which had previously only been obtained from animal sources.

Karrer [2] classes glycyrrhizic acid with the glucosides. He gives the products of hydrolysis as glycyrrhetic acid (1 molecule) and glycuronic acid lactone (2 molecules). Analyses indicate that glycyrrhetic acid has the formula $C_{45}H_{72}O_6$, or possibly $C_{44}H_{70}O_6$.

Insect flowers.

Insect or pyrethrum flowers (*Chrysanthemum cinerariæfolium*) contain a viscous oil, with highly insecticidal properties, which has been termed "pyrethrone." More recently [3] two active constituents termed *pyrethrine I.* and *pyrethrine II.* have been isolated from "pyrethrone." The pyrethrines are esters of a ketonic alcohol, pyrethrone, combined with one or other of two complex carboxylic acids. Neither the alcohol nor the acids have insecticidal properties, although the esters are exceedingly active, pyrethrine I. being capable of killing moths at a dilution of 1 in 10,000 in 10 to 20 minutes.

[1] *Arch. Pharm.*, 1907, **245,** 97; 1908, **246,** 545; 1909, **247,** 121.
[2] P. Karrer, W. Karrer, and Chao, *Helv. Chim. Acta*, 1921, **4,** 100.
[3] Staudinger and Ruzicka, *Helv. Chim. Acta*, 1924, **7,** 177.

Vitamins.

It has long been known that a diet of proteins, carbohydrates, fats, and mineral salts is not sufficient to maintain normal health, unless accompanied by small quantities of substances which have been variously described as "vitamines," "vitamins," or "accessory food factors." Our knowledge of these substances has been chiefly obtained from a study of the deficiency diseases which result from their absence.[1]

Early in the present century it was found that the more thorough polishing of the rice, which together with fish forms the staple food of the natives of the Philippine Islands, resulted in a great increase in the disease beri-beri. In 1907 Fraser and Stanton discovered that the matter removed from the rice (the so-called "rice-polishings") prevented the development of the disease when added to the diet. In 1911 Funk fractionated rice-polishings, and obtained a highly active fraction for which he coined the name "vitamine," and which was found to be capable of curing polyneuritis of birds, a disease which is recognised as the equivalent of human beri-beri. Previous to this (in 1906), Hopkins had come to the conclusion that the growth of laboratory animals demanded something in foods that could not be accounted for among the ordinary nutrients. To these hypothetical substances he gave the name "accessory food factors."

At least five vitamins are now well recognised, and are distinguished by the letters A, B, C, D, and E. The table on opposite page summarises the main sources of the different vitamins, and the diseases which develop in their absence.

Vitamins occur in foodstuffs in very minute quantities, and it is only on account of their profound physiological effects that they have been recognised. Foodstuffs are standardised on their vitamin content by experiments on animals. Briefly, animals are fed on a diet which is complete in every respect except for the particular vitamin under consideration. Deficiency symptoms gradually develop, and when these are sufficiently marked the substance under examination is added to the diet, and the curative effect noted.

[1] A valuable general account of vitamins is given by Carr, *J. Soc. Chem. Ind.*, 1926, **46**, 945.

VITAMINS.

Vitamin.	Solubility.	Disease Developed in Absence of Vitamin.	Present in	Absent from
A[1]	Oil-soluble	Xerophthalmia	Cod-liver oil, cream, green vegetables.	Vegetable oils.
B	Water-soluble	Polyneuritis	Yeast, seed germs, nuts, meat, milk, marmite.	White bread.
C	Water-soluble	Scurvy	Lemon and orange juices, cabbage, meat, milk.	Preserved foods.
D[1]	Oil-soluble	Rickets	Cod-liver oil, cream, green vegetables.[2]	Vegetable oils.
E	Oil-soluble	Sterility	Wheat germ oil, lettuce, peas.	Cod-liver oil, animal fats.

Vitamin A is synthesised by plants, and is present in green leaves and the embryos of many seeds. Fish, in common with animals, probably derive the whole of their vitamin A directly or indirectly from the vegetable kingdom.

The United States Pharmacopœia describes an assay process for vitamin A in cod-liver oil. The method is based on the estimation of the minimum amount of cod-liver oil necessary to meet specific growth-promoting requirements in standard test animals. The unit is described as the minimum daily amount of cod-liver oil required to cure induced symptoms of vitamin A starvation in young albino rats, and to cause a gain in weight of 10 to 20 grams within a period of thirty-five days, under specified conditions of growth and diet. It should be noted that the unit is not a measure of the anti-rachitic activity of cod-liver oil. The method is not now considered satisfactory,[3] because no attempt is made to ensure that all reserves of both vitamin A and vitamin D are used up. (The body reserve of A is greater than that of D, and growth stops when the reserve of either A or D is used up.)

[1] Vitamins A and D are together responsible for growth.

[2] Vitamin D may also be produced in the body by irradiation with ultra-violet light.

[3] Chick, *Biochem. J.*, 1926, **20**, 119.

Vitamin A may be recognised by the intense blue colour it yields with antimony trichloride in chloroform solution. This test is used colorimetrically to compare the vitamin A contents of different samples of cod-liver oil, and there is little doubt that the intensity of the colour gives an actual measure of the vitamin A content.[1]

Detection of vitamin A.—Dissolve a few drops of cod-liver oil in chloroform, and add a solution of antimony trichloride in chloroform. Note the intense blue colour.

Vitamin B.—Considerable evidence now exists in support of the view that vitamin B consists of two factors :—[2]

1. An anti-neuritic or anti-beri-beri factor.
2. A pellagra-preventing factor (Goldberger's P.P.).

The two components of vitamin B have been described as vitamins F and G.[3]

Vitamin C.—It has been known for generations that lack of green vegetables, such as occurred during long sea voyages in the days of sailing ships, gives rise to scurvy, and that lime, orange, or lemon juice has a definite curative action in this disease. It is now known that scurvy is a deficiency disease, caused by lack of vitamin C.

It is a remarkable fact that some animals, such as rats, mice, and rabbits, do not acquire scurvy, even if completely deprived of vitamin C.

Vitamin D.—Vitamin A was formerly believed to be the anti-rachitic agent in cod-liver oil, but the anti-rachitic properties of the oil are now known to be due to vitamin D.

When cholesterol (present in animal fats, see p. 20) is exposed to ultra-violet light, it develops the anti-rachitic properties characteristic of vitamin D. The activity is actually acquired by an impurity known as *ergosterol*, which is present in crude cholesterol. "Irradiated ergosterol," manufactured from ergosterol extracted from yeast fat or ergot, may have as much as 200,000 times the anti-rachitic activity of good cod-liver oil.

Vitamin E has not yet been fully investigated.

[1] See Carr and Price, *Biochem. J.*, 1926, **20,** 497 ; also Rosenheim, *ibid.*, 1927, **21,** 1329.

[2] See Chick and Roscoe, *Biochem. J.*, 1927, **21,** 698 ; Salmon, *J. Biol. Chem.*, 1927, **73,** 483.

[3] See Sherman and Axtmayer, *J. Biol. Chem.*, 1927, **75,** 207.

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